Environmental Factors Altering Thyroid Function and Their Assessment

by Charles P. Barsano*†

Chronic ingestion of modest doses of dietary iodine, radiation, and polychlorinated biphenyls (PCB's and PBB's) are environmental factors with known or suspected adverse effects on the human thyroid. Iodine consumption in the United States is approaching 1 mg daily for a large segment of the population. Data are reviewed which support the need for concern regarding the long-term adverse effects of dietary iodine on thyroid function, particularly in certain susceptible individuals. Environmental sources of radiation pose a significant risk of thyroid cancer and hypothyroidism under certain circumstances which may be intentional, inadvertent, or accidental. Exposure to polychlorinated biphenyls during manufacture or as industrial pollutants are hazardous to man and to wildlife in moderate or large quantities and perhaps also in small amounts. The need to investigate the potential harm posed by these factors in the quantities commonly encountered is emphasized.

A wide variety of environmental agents adversely affect the thyroid gland. Some have been precisely identified while others are not well characterized. Some are known to alter thyroid function under unusual circumstances, but are only suspect in the quantities ordinarily encountered. This review will be limited to several agents whose occurrence within the environment is a by-product of technology and whose effects may potentially extend to a large number of people. Initially, the adverse effects of environmental toxins on thyroid function will be discussed with emphasis on their clinical and laboratory evaluation. Subsequent sections of this review will concern the adverse thyroidal effects, proven or suspected, of modestly high dietary iodine consumption, environmental sources of radiation, and polychlorinated biphenyl exposure.

Assessment of Thyroid Toxicity

Categorically, the major thyroidal abnormalities include hypothyroidism, hyperthyroidism, goiter, and carcinoma. Environmental agents which adversely affect the thyroid assume clinical importance by their ability to induce any one or more of these problems. None are unique to environmental toxins and consequently evaluation of suspected environmental toxin-related thyroid disease proceeds along the same diagnostic routes as does the investigation of spontaneously occurring thyroid disease.

Hypothyroidism is suggested clinically by inexplicable fatigue, cold intolerance, menstrual irregularities, or constipation, among a wide variety of other nonspecific symptoms. A goiter may be present on physical examination. Hyperthyroidism is characterized by nervousness, weight loss, heat intolerance, or palpitations, among other symptoms. A goiter or nodular thyroid is usually present on examination. Smooth or nodular goiters are associated with a variety of thyroid diseases and do not imply concurrent hypofunction or hyperfunction. If present, symptoms are usually attributable to hypo- or hyperthyroidism. Large goiters may pose cosmetic problems or present with symptoms suggestive of tracheal compression. Thyroid cancer is considered in the differential diagnosis of a palpable thyroid nodule; positive diagnosis is made histologically after biopsy or surgical excision. Thyroid cancer patients are generally euthyroid and asymptomatic.

The laboratory evaluation of subjects with suspected thyroid dysfunction, goiter, or potentially malignant nodules is illustrated in Figure 1. Serum thyroxine (T₄), serum triiodothyronine (T₃), free T₄, and their...
Thyroid cysts and benign adenomata may also appear as scintographically hypofunctional areas. With occasional exceptions, functioning nodules are benign. Additional diagnostic information is offered by the degree of thyroid nodularity. A single nodule in an otherwise normal thyroid is more likely to be malignant than a nodule in a uniformly multinodular gland.

Ultrasoundography (1) is a valuable noninvasive diagnostic technique for distinguishing solid thyroid nodules from simple cysts, the latter being much less likely to be malignant. Needle aspiration biopsy (2) yields much the same information plus additional cytological data concerning the malignant potential of the cells.

A radioactive iodine uptake (RAIU) determination is often useful in the evaluation of hyperthyroidism. Factitious hyperthyroidism (self-induced by excessive thyroid hormone ingestion) and "silent" or "painless" thyrotoxicosis (3-5) are accompanied by a very low RAIU, whereas the more common forms of hyperthyroidism are associated with normal or elevated RAIU's.

The primary discriminants of toxin-related thyroid disease are historical and epidemiological. On an individual basis the onset of detectable thyroid abnormalities must be carefully considered with respect to the earliest exposure to the suspected toxin. Similarly, the amelioration of symptoms should be considered in terms of the time after cessation of exposure. On a statistical basis the type and prevalence of the suspected thyroidal abnormality within an exposed population should be compared to these same parameters in a comparable but unexposed population.

A family history of thyroid disease should always be obtained from individuals suspected of environment-related thyroid disease. Dys hormonogenetic goiters and autoimmune thyroid diseases exhibit significant hereditary predispositions. Their recognition may suggest that the suspected thyroid abnormality pre-existed the toxic exposure and was induced to become clinically apparent. Certain individuals may be essentially free of disease prior to exposure but are more susceptible to developing thyroidal abnormalities in response to toxic insults than ordinary individuals.

**Chronic Ingestion of Modest Doses of Dietary Iodine**

Prior to dietary iodine prophylaxis, goiter, hypothyroidism, and cretinism from iodine deficiency had been endemic in many areas of the world. In many areas these problems still exist (6). In the United States, goiter had been particularly preva-
lent along the northern border of the country and in the upper midwestern states. Since the introduction of iodized salt in these areas in the 1920's (7), the prevalence of goiter has been dramatically reduced (8). By 1970, daily iodine consumption in the U.S. ranged from 238 μg to 738 μg (9), as calculated from its effects on the normal ranges of radiiodine uptakes at various centers around the country. Daily iodine consumption in endemic iodine-deficiency areas estimated by direct assay of iodine in 24-hr urine specimens is usually less than 50 μg. The U.S. Recommended Dietary Allowance (RDA) for iodine has most recently been set at 150 μg daily for adults plus an additional 25 μg and 50 μg for pregnant and lactating women, respectively (10). Consistent with these determinations, iodine-deficiency in this country is no longer a public health problem.

To the contrary, more recent estimates of daily iodine consumption in the U.S. and Canada indicate that iodine consumption is clearly above the RDA and for most people substantially above the RDA (Table 1). A study of children aged 9-16 in Michigan, Kentucky, Texas, and Georgia in 1971-72 revealed an average iodine intake of 459 μg per day (11). An extensive study in 1968-70 covering 36,000 people in ten states revealed that 9.5-21.9% of the people tested excreted in excess of 799 μg iodine per gram of urinary creatinine per day in 7 of the 10 states (12). As approximately one-half of the studied population in the seven states were adults [estimated to excrete approximately 1.2 g (females) to 1.5 g (males) creatinine per day], it can be grossly estimated that 5-10% of the test population, or 10-20% of the adults, consumed over 1 mg of iodine per day. A 1970-72 nutritional survey of Canada revealed that approximately 5% of the adult population consumed 500-700 μg iodine/g urinary creatinine, or in the order of approximately 0.8 mg iodine per day. Perhaps 2% of the population consumed in excess of 800 μg iodine/g creatinine, or in excess of 1 mg of iodine per day (13). Over 15 years ago, healthy individuals near Washington, D.C. were calculated to consume over 0.8 mg of iodine daily, ranging up to 1.5 mg per day, on 20% of days studied (14). Analysis of the adult Market Basket Surveys of 1974 and 1975 indicate an average daily iodine intake of 784 μg and 642 μg, respectively, in those consuming a 2800 calorie diet (15). Addition of 260 μg of iodine from 3.4 g of iodized table salt (16) brings the average daily iodine intakes to approximately 1 mg per day. As a result of the studies involving direct measurement of plasma or urinary iodide and the observations of progressively declining normal ranges for radioactive iodine uptakes (17-19), the trend toward increased iodine consumption in the U.S. has not gone unrecognized (15, 20-21).

Although it is very difficult to project an estimated average daily iodine consumption for children and for adults in the U.S. in 1980, it is probably fair to assume that at least 10% of the adult population, and possible much more, consume in excess of 1 mg iodine per day and that a comparable percentage of children may be consuming an iodine load proportionate by body weight to the adult consumption. Since it can be calculated that approximately 260 μg of iodine are consumed daily in table salt iodized at the 1:10,000 level (100 μg KI/g salt or 75 μg iodide/g salt), it becomes apparent that most ingested iodine is obtained from less obvious dietary sources (16). Ingestible iodine is commonly found in a wide variety of foodstuffs, food coloring and seasonings, food processing agents, and medicaments. The bulk of dietary iodine, however, is probably derived from milk and other dairy products and from bread prepared with iodate as a dough conditioner (15). The many and diverse uses for iodine in the food and dairy industry give reason to suspect that dietary sources of iodine are not likely to decline until an equally diverse group of alternative agents are identified and implemented.

At present it is impossible to be certain that chronic ingestion of modest amounts of iodine would have adverse effects on thyroid function although there is considerable evidence that supports the wisdom for concern. If even a few percent of the population ingest in excess of 1 mg of iodine per day...
daily, substantial numbers of people are involved. Certain potentially susceptible groups of people, e.g., the unborn and those with subclinical thyroid disease, may face a slight but unrecognized risk from quantities of iodine too little to affect ordinary individuals. As depicted in Figure 2, interpretation of the large body of data relevant to the adverse effects of iodine on thyroid function requires appreciation of the baseline daily iodine ingestion of the subject population, the daily quantity of iodine to which the subject population is being introduced, the rate of introduction of increased levels of iodine into the population, the presence and nature of any underlying susceptibilities to overt thyroid dysfunction, and the type of thyroid abnormalities reported to result from the exposure.

There are numerous reports of iodine-induced hyperthyroidism (Jod-Basedow phenomenon) when iodine, sometimes in quantities less than 1 mg daily (24), were introduced into iodine-deficient populations (25, 26). Subsequent study (27) support the theory that the induced hyperthyroidism is a manifestation of underlying autonomously-functioning thyroid nodules or Graves' disease. Assumedly, the underlying disease had been silent only for lack of available substrate for thyroid hormone production. Administration of ordinary amounts of iodine (several hundred µg per day) to subjects in areas of minimally adequate quantities of dietary iodine, e.g., parts of western Europe, has been reported to induce hyperthyroidism in subjects with nodular thyroids (28) and in some individuals without apparent underlying thyroid disease (29). It does not follow, however, that this phenomenon would be reproduced by superimposing comparably small amounts of iodine on a population which has been chronically exposed to more than adequate sources of iodine.

There are reports of thyroid dysfunction arising in subjects living in iodine-sufficient areas (greater than 100 µg iodine per day). With very few exceptions the reported cases involve administration of pharmacological doses of iodine, here regarded as greater than 10 mg per day but generally in excess of 100 mg per day. Ingestion of large quantities of iodine by pregnant women is well known to induce goiter (30, 31) and less commonly hypothyroidism (31, 32) in the fetus. At times these goiters have resulted in tracheal compression and neonatal asphyxiation. Normal individuals are also at a small but definite risk of developing goiter and occasionally hypothyroidism during chronic ingestion of pharmacological doses of iodine (30, 33, 34). Perhaps most well known are the residents of coastal areas of Hokkaido, Japan who consume 8-200 mg of iodine per day (35). School children of these areas maintain a 25% prevalence of goiter. Patients with chronic obstructive pulmonary disease (36) or cystic fibrosis (37) treated with 450 mg of iodine or more per day have been reported to develop goiter, often associated with hypothyroidism.

Hypothyroidism has also been described as a primary consequence of the administration of large doses of iodine to euthyroid individuals in iodine-sufficient areas. Four of seven euthyroid patients with underlying Hashimoto's thyroiditis became hypothyroid within 4-6 weeks of treatment with 180 mg of iodine per day (38). Patients with hyperplastic or regenerating thyroid tissue as seen after partial thyroidectomy for thyroid nodules (39) or Graves' disease (33, 38) or after radioactive iodine therapy of Graves' disease (33, 40, 41) have also been shown to become hypothyroid after the administration of large doses of iodine.

The induction of hyperthyroidism in iodine-sufficient individuals by large doses of iodine has

Environmental Health Perspectives
also been reported. Patients with euthyroid nodular goiters have been shown to become hyperthyroid after several weeks of treatment with 180 mg iodine per day (42). An asthmatic child with a family history of goiter and hyperthyroidism, treated with well over 1000 mg of iodine per day, was observed to become thyrotoxic within four months of initiation of treatment and improved promptly after discontinuation of the medication (43). Iodine derived from radiographic contrast media has also been reported to induce hyperthyroidism in a patient with a nontoxic, autonomous thyroid nodule (44). But the potential for pharmacological doses of iodine to induce goiter, hypothyroidism or hyperthyroidism in iodine-sufficient healthy individuals, or even in susceptible individuals, may not necessarily be applicable to modest doses of iodine in the 1-10 mg per day dosage.

It should be noted that relatively small doses of 0.5 mg iodine are capable of inducing abnormal perchlorate discharge tests in some euthyroid patients with mild Hashimoto's disease (38, 45) and that this characteristic may identify which of these patients are prone to become hypothyroid after treatment with large doses of iodine (38). The same phenomenon has been observed in euthyroid patients previously treated with radioactive iodine for Graves' disease (33). It does not follow, however, that chronic exposure of patients with subclinical disease to a diet incremented by 0.5 mg of iodine per day would necessarily lead to clinically apparent disease. Interestingly, this dose of iodine has been alleged to induce hyperthyroidism in one patient within several weeks (46).

The effects on thyroid function of chronic iodine consumption in the 1-10 mg per day range have not been adequately investigated. A most informative study concerning this topic involves a prison population whose source of drinking water contained 0.5 mg/l. of iodine as a disinfectant (47, 48). Daily iodine consumption was probably in the order of 1-2 mg daily for up to 3 years. Not surprisingly, their 24-hr radioactive iodine uptakes dropped from an average of 17% to 7.2% without change in the serum thyroxine levels. No cases of goiter or hypothyroidism were thought to result from this exposure, although four inmates who may have had mild symptoms of hyperthyroidism when entering prison became frankly thyrotoxic during their imprisonment. Two patients exhibited elevations in their serum thyroxine levels after discontinuing the water, but normalized their thyroxine levels when again exposed the water. Importantly, no neonatal goiters or increased incidence of congenital anomalies were observed in 181 full-term neonates of imprisoned mothers.

The findings of several studies suggest that increases in iodine consumption may favor induction of Hashimoto's thyroiditis. The prevalence of histologic thyroiditis in thyroidectomy specimens appears to have increased after the introduction of iodine prophylaxis in the United States (49-51). Lymphocytic thyroiditis was rarely found in thyroid specimens of untreated patients with iodine-deficiency goiters in the Himalayas (52). Administration of large amounts of iodine to rats and hamsters has been reported to induce lymphocytic infiltration of the thyroid (53, 54). Addition of iodine to immunogenic preparations of thyroid extracts has also been shown to induce a histologically more humanlike lymphocytic thyroiditis in beagles (55). However, the animal models may not be equivalent to the human disease. The prevalence of physical and laboratory features of Hashimoto's thyroiditis and Graves' disease in contemporary school children (11, 56, 57) is surprisingly high but not of itself indicative of a causative or exacerbating role for iodine. These and other studies have been previously considered with the general impression that the evidence for a role of iodine in the pathogenesis of chronic lymphocytic thyroiditis remains inconclusive (23).

The induction by iodine of goiter or abnormal 131I uptake and perchlorate discharge tests in patients with Hashimoto's thyroiditis rather argue that these patients are particularly susceptible to the adverse effects of iodine, perhaps less capable of escaping the Wolff-Chaikoff block (58). It has been suggested that iodides enhance a pre-existing intra-thyroidal organization defect in patients with Hashimoto's thyroiditis (59).

Other adverse effects of modest iodine ingestion have been suggested. The increasing consumption of iodine over the 10-year period from 1962 to 1972 has been hypothesized to effect a reduction in the remission rate of antithyroid drug therapy of Graves' disease (60). Administration of iodine to patients withdrawn from antithyroid drugs has had somewhat conflicting effects on remission rates (61, 62). The relatively high incidence of papillary thyroid cancer in Iceland and Japan, two countries with relatively high daily iodine consumption, has been pointed out (63, 64), but the putative association of thyroid cancer and increased iodine consumption is open to other interpretations (23). Acne, ioderma, and a wide variety of adverse effects not related to the thyroid have been thoroughly reviewed elsewhere (65).

At present the evidence that chronic iodine intake in the order of 1-10 mg daily presents a significant risk of thyroid dysfunction is largely circumstantial but, in view of the size of the
potential target population, the trend toward increased iodine consumption, and the more probable success of earlier rather than later intervention, the question merits serious evaluation. This issue has, in fact, been the topic of a recent workshop (66). Recommendations forthcoming from this workshop are anticipated to include an appeal to limit further increases in dietary iodine input until the biological safety of chronic, modest iodine ingestion is more firmly established.

Environmental Sources of Radiation

There is little doubt that under appropriate circumstances radiation exposure can induce a variety of thyroid-related abnormalities. Treatment of hyperthyroid patients with \(^{131}I\) has been observed to exacerbate the hyperthyroidism (67, 68), presumably by releasing stored hormone from radiation-damaged tissue. There are numerous reports of primary hypothyroidism arising after radiation exposure to the thyroid (69, 70). High radiation doses (> 1,000 rem) to the thyroid administered as \(^{131}I\) for the treatment of Graves’ disease (40) and cardiac disease (71, 72), or as external radiation to the head and neck for regional carcinoma (69, 70, 73) are known to induce hypothyroidism particularly at very high dosages (> 25,000 rem). Exposure to external radiation less than several hundred rem appears to involve very little risk of hypothyroidism (74-76), although a threshold as low as 20 rem has been suggested (69) for \(^{131}I\) exposure.

Induction of thyroid cancer by radiation has been considered under a wide variety of circumstances. As outlined in Table 2, radiation exposure can be intentional, inadvertent, or accidental. Intentional destruction of thyroid tissue with administration of \(^{131}I\) is a common and effective therapy for Graves’ disease and was formerly used for the amelioration of angina pectoris (71). In smaller doses \(^{131}I\) and \(^{123}I\) are often used in diagnostic thyroid scans and uptake measurements. Typical thyroid radiation exposures from these procedures are given in Table 3.

| Procedure               | Dose   | Exposure (rads)* |
|-------------------------|--------|------------------|
| \(^{131}I\) treatment of angina | 30 mCi | 30,000           |
| \(^{131}I\) treatment of Graves’ disease | 5 mCi | 5,000            |
| \(^{131}I\) scan          | 50 µCi | 50               |
| \(^{131}I\) uptake        | 6 µCi  | 6                |
| \(^{123}I\) scan          | 300 µCi| 2                |
| \(^{123}I\) uptake        | 50 µCi | 0.4              |
| \(^{99mTc}\) scan         | 3,000 µCi| 1                |

* Rads are equivalent to rems for radioisotopes of iodine.

Radiation exposure to the thyroid in excess of approximately 25,000 rem involve a significant risk of inducing hypothyroidism but seems to involve minimal risk of carcinogenesis when employed for the relief of cardiac disease (69, 84, 85). Expectedly, lethal doses of radiation would greatly reduce the population of cells available for carcinogenesis. The lesser degree of radiation exposure to the thyroid involved in the treatment of Graves’ disease with \(^{131}I\), generally 5,000-10,000 rem, similarly does not appear to involve a significant risk of carcinoma. A number of studies (86-89) indicate that carcinogenesis is not a significant risk at doses in excess of approximately 2000 rem, and that \(^{131}I\) therapy for Graves’ disease does not impose a risk of carcinogenesis (85, 90, 91).

Radiation exposure from diagnostic \(^{131}I\) thyroid scans is considerably less than therapeutic exposure but is perhaps not insignificant. A 50 µCi \(^{131}I\) scan would deliver an approximate exposure of 80 rem to an adult thyroid and two or three times that to a child’s thyroid (92). The studies of Rallison and others (75, 79) on the schoolchildren exposed to comparable amounts of radiation from nuclear testing suggests that 50-100 rem may approximate the threshold below which there is no appreciable risk of carcinogenesis. One case of thyroid carcinoma...
following diagnostic studies has been reported (93). Available information suggests that 131I scans approach the exposure level thought to pose a probable though small risk of carcinogenesis.

Radiation therapy of lymphomatous cervical lymph nodes or other carcinomas of the head and neck may involve considerable exposure to the thyroid, often enough to result in primary hypothyroidism (79). Anecdotal cases of thyroid cancer in patients previously subjected to radiotherapy of head or neck carcinoma have been noted in several reports and letters (94-99) as well as in the author's own experience. Likely, the generally higher radiation exposure and older age of those subjected to radiotherapy of head or neck malignancy account for the lower incidence of thyroid cancer in these patients.

In the 1940's and 1950's low-dose radiotherapy was commonly used for a variety of benign problems of infancy and childhood (77). Depending on the dose of applied radiation and the proximity of its field to the anterior neck, thyroid exposure could range from virtually nil to over a thousand rem. It was subsequently observed that children with thyroid cancer had a frequent history of prior radiation for benign problems (100-102). Since then, numerous reports have confirmed the association of low-dose radiation exposure and thyroid cancer (76, 103-106). Analysis of several studies demonstrate a dose-dependent risk of post-radiation carcinogenesis up to approximately 1000-1500 rem (69, 86, 107). It is unclear if radiation exposures below 20 rem are associated with a risk of carcinoma (74).

The latent period for detection of thyroid carcinomas after radiation exposure is generally ten or more years and may extend up to or beyond 40 years (76, 86, 97, 108-110).

Radiation exposure from nuclear weapons includes both direct, external radiation and exposure from absorbed or ingested radioisotopes of iodine (particularly 131I) derived from the fallout. Survivors of the Hiroshima and Nagasaki A-bomb blasts studied 13-16 years after exposure were not found to exhibit a greater prevalence of thyroid cancer when compared to a contemporary non-exposed clinic population, although the prevalence of thyroid cancer among the exposed patients appeared to be inversely proportional to their distance from the hypocenter of the blast (82). In a subsequent study (81) of the A-bomb survivors 13-26 years after the blasts, the prevalence of thyroid cancer was indeed found to be higher in all those exposed to 50 or more rads of radiation, particularly if the individuals were less than 20 years of age at the time of exposure.

Of 67 Marshall Islanders inadvertently exposed to direct gamma-radiation and to 131I, 132I, 133I, and 135I fallout, 21 developed thyroid abnormalities including three malignancies, 16 benign nodules, and two cases of hypothyroidism (78). The adult exposure on the first day was in the order of 160 rads from 131I and 175 rads from gamma-radiation. Children under age 10 seemed to have a much higher propensity to develop a thyroid abnormality, possibly as a result of their generally threefold higher radiiodine exposure. It may also be true that thyroid tissue in children is more susceptible to radiation damage than adult tissue (111).

Infants and children aged 8 or less at the time of exposure to the fallout in southwestern Utah following the Nevada nuclear weapons tests in the early 1950's were found to have no greater prevalence of thyroid nodularity than a control, non-exposed population (79). The target population was studied approximately 10 years after an estimated thyroid exposure of 5-50 rads and more than 100 rads in some cases. Radiation exposure from the Nevada tests was thought to be largely acquired from 131I-contaminated milk. Minute doses of radioactivity have also been detected in fetal human thyroids after maternal exposure to 131I-containing fallout from the nuclear weapons testing in 1958 by the United States, Great Britain, and the Soviet Union (112).

Accidental ingestion of 131I or 125I has occurred in laboratory technicians during radio-iodination procedures for labeling proteins. Ingested doses could range from the trivial to several millicuries. The latter situation would to some extent mimic the treatment of Graves' disease although iodine turnover and tissue sensitivity to radiiodine would be lower in normal thyroid glands. In a study comparing the efficacy of 125I treatment of Graves' disease to that of 131I, the former isotope resulted in a greater degree of hypothyroidism (113).

Nuclear reactor accidents have the potential of exposing many people to significant amounts of thyroid radiation exposure. Huge amounts of volatile and water-soluble radioisotopes of iodine can be generated, of which 131I and 133I are the most important (114). Fortunately, in the recent mishap at the Three Mile Island Nuclear Station in March, 1979, the preponderance of radiiodine isotopes was well contained. In a preliminary study (83) in which milk samples in the immediate area were assayed for 131I, only one-fourth of the samples contained the isotope in concentrations ranging from 1-41 pCi/l. It was calculated that an infant drinking 1 liter of the most heavily contaminated milk would be subjected to 5 mrem of thyroidal radiation; an adult consuming the same quantity would be subjected to only one-tenth that amount.
These exposures are well below the estimated annual total body radiation exposure from unavoidable sources of cosmic and terrestrial radiation. Estimated $^{131}$I intake from the air was similarly miniscule. Radiation-associated hyperthyroidism, hypothyroidism, and carcinogenesis are not clinically distinct from the spontaneously occurring thyroid diseases. Except perhaps for the histological features of radiation-fibrosis or radiation-thyroiditis, the etiology of the radiation-associated thyroid abnormalities become apparent only by uncovering the historical and epidemiological features of radiation exposure in affected individuals.

**Polyhalogenated Biphenyls**

Polyhalogenated biphenyls are commonly used compounds with a wide variety of industrial applications. Polychlorinated biphenyls (PCB’s) have been used as flame retardants. Polybrominated biphenyls (PCB’s) are used as lubricants, adhesives, inks, hydraulic fluids, and as plasticizers (115). The environmental impact of the PCB’s derives from their presence as pollutants in lakes and rivers and their capacity to accumulate in the adipose tissue of fish and fish-eating predators, including man (115). There is little question that the PCB’s affect the thyroid function of animals. Extensive (116-118) and brief reviews (119) of the social and biological impact of the PCB’s are already available, and so this review will focus primarily on the studies pertinent to the potential adverse effects on human thyroid function.

The preponderance of animal data implicate the PCB’s as inducers of goiter and hypothyroidism. Coho salmon from the Great Lakes have exhibited a high prevalence of goiter in recent years (120-122). The very low iodine content of the Great Lakes compared to sea water (123) is probably partially responsible for the goiters in these fish. It has been demonstrated decades ago that rainbow lake trout were more commonly goitrous than those found off California (124). Recent analysis reveals that the frequency of Coho salmon goiter is not inversely proportional to the iodine content of the lakes from which the Coho were obtained (122). Further, the incidence of goiter among the Coho population appears to be increasing in recent years, whereas the iodine content of the water is essentially stable. These observations are consistent with the interpretation that the increasing incidence of goiter reflects increasing lake pollution (not necessarily limited to PCB’s). It has also been shown that PCB’s are capable of inducing thyroid abnormalities when fed to Coho (123). As consumers of other fish, and perhaps being less well adapted to a low iodine environment than fish indigenous to the Great Lakes, the Coho are more likely to accumulate fat-soluble goitrogens and may be more susceptible to goitrogenesis. In addition to goiter, the Coho have exhibited markedly depressed thyroxine and triiodothyronine levels (121). Histological features suggestive of thyroid cancer have also been reported (120).

The molecular mechanisms of PCB-induced goitrogenesis and hypothyroidism have been systematically studied in rats cutaneously exposed to PCB-containing immersion oil (125). Compared to unexposed controls, the PCB-exposed animals exhibited decreased serum thyroxine ($T_4$) but not triiodothyronine ($T_3$) levels. It appeared that PCB displaced $T_4$ from the serum proteins, accounting for the low total $T_4$ levels. Additionally, increased biliary excretion and loss of $T_4$, possibly related to the induction of $T_4$-UDP-glucuronyl transferase, may have contributed to the simultaneously reduced free $T_4$ index. Enhancement of peripheral $T_4$ to $T_3$ conversion was thought to explain the absence of simultaneous reductions in the serum $T_3$ level and free $T_3$ index. Thyroid enlargement has also been observed in rats treated with PCB’s (126) or PBB’s (127).

After long-term contact with PCB in more than trace quantities, humans may develop an acnelike skin rash, weakness, headaches, gastrointestinal disturbances, irritation of the eyes, nose and throat, swollen extremities, and many other symptoms (128, 129). In 1968, over 1000 people in southwestern Japan were afflicted with a syndrome, usually beginning with a chloracneline skin eruption now known as Yusho disease. The epidemic was traced to PCB-contaminated rice oil used for cooking (129). Subsequently, 22 deaths were associated with the PCB exposure, including nine malignancies of various types (128). No specific thyroid abnormalities were reported.

PCB is present at 5 mg/kg in lake fish (115) and is also found in the adipose tissue of a surprising 50-45% of the general public (130, 131). It is uncertain, however, if there are any adverse health effects pursuant to this order of exposure. Hematologists technicians working with PCB-containing microscope immersion oil exhibited no abnormalities when screened for decreased serum $T_4$ levels and increased thyrotropin levels as indicators of early hypothyroidism (125). A recent evaluation of 35 workers in a PBB manufacturing plant (132) identified four cases of primary hypothyroidism, whereas no cases were found among 89 control subjects. These same four cases had markedly elevated titers of antithyroid microsomal antibodies.
suggesting that the hypothyroidism was a manifestation of chronic lymphocytic thyroiditis, perhaps a PBB-induced exacerbation of pre-existing but subclinical disease. There was not statistically significant difference in the prevalence of elevated antithyroid antibody titers between the control and exposed groups. PBB's also have been reported to cause decreased serum T₄ levels in rats (127).

In a subsequent report, 51 subjects were evaluated who had been exposed to PBB's and found to have abnormal serum or adipose levels of this compound (133). Neither thyroid nodularity or goiter, nor unusual incidence of abnormal serum T₄, thyrotropin or T₃-resin uptake were found. As suggested, the absence of abnormalities must be viewed with the understanding that PBB's may have a long latent period and falsely appear innocuous. The evidence for harm by PCB and PBB exposure in the quantities commonly encountered by the average person is still inconclusive.

In parallel to the potential hazards perceived for the chronic ingestion of modest amounts of iodine, individuals with greater than average exposure and those with a greater susceptibility to the compounds are likely to be the first to manifest goiter or hypothyroidism.

**Conclusion**

The recurrent theme in the consideration of iodine, radiation, or polyhalogenated biphenyls as environmental thyroid toxins in the quantities commonly encountered is that there appears to be abundant evidence for suspicion but scant evidence for definitive conclusions. In part this may reflect our intrinsically more rapid capacity to apply technology than to evaluate it, but also reflects the lag phases from the introduction of an agent into the environment to the uncovering of specific and relevant questions concerning its impact, and from the recognition of relevant questions to the determination of the answers. With each of these agents it is hoped that the important questions concerning their thyroid toxicity have been recognized and that the answers will be adequately pursued.

This work was supported by U.S. Public Health Service Grants AM-13377 and AM-06151.

**REFERENCES**

1. Blum, M., Goldman, A. B., Herskovic, A., and Hernberg, J. Clinical applications of thyroid echography. N. Engl. J. Med. 287: 1164 (1972).
2. Walsh, P. G., Hazani, E., Strawbridge, H. T. G., Mislin, M., and Rosen, I. B. Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. Ann. Intern. Med. 87: 270 (1977).
3. Papapetrou, P. D., and Jackson, I. M. D. Thyrotoxicosis due to "silent" thyroiditis. Lancet 1: 361 (1975).
4. Gluck, F. B., Nusynowitz, M. L., and Plymate, S. Chronic lymphocytic thyroiditis, thyrotoxicosis, and low radioactive iodine uptake. N. Engl. J. Med. 293: 624 (1975).
5. Woolf, P. D., and Daly, R. Thyrotoxicosis with painless thyroiditis. Am. J. Med. 60: 73 (1976).
6. Stanbury, J. B., and Hetzel, B. S., Eds., Endemic Goiter and Endemic Cretinism. Wiley, New York, 1980.
7. Kimball, O. P. The prevention of simple goiter in man. Am. J. Med. Sci. 163: 634 (1922).
8. Brush, B. E., and Altlund, J. K. Goiter prevention with iodized salt: results of a 30-year study. J. Clin. Endocrinol. Metab. 12: 1380 (1952).
9. Oddie, T. H., Fisher, D. A., and Thompson, C. S. Iodine intake in the United States: a reassessment. J. Clin. Endocrinol. Metab. 50: 659 (1979).
10. Recommended Dietary Allowances, Ninth Revised Edition. National Academy of Sciences, Washington, D.C., 1980.
11. Towbridge, F. L., Matovinovic, J., McLaren, G. D., and Nichaman, M. Z. Iodine and goiter in children. Pediatrics 56: 82 (1975).
12. Towbridge, F. L., Hand, K. A., and Nichaman, M. Z. Findings relating to goiter and iodine in the Ten-State Nutritional Survey. Am. J. Clin. Nutr. 28: 712 (1975).
13. Nutrition Canada. The Saskatchewan Survey Report. Bureau of Nutritional Sciences, Department of National Health and Welfare, Information Canada, Ottawa, 1975.
14. Vought, R. L., and London, W. T. Iodine intake and excretion in healthy subjects. Am. J. Clin. Nutr. 16: 124 (1965).
15. Harland, B. F., Johnson, R. D., Blendedmann, E. M., Prosky, L., Vanderveen, J. E., Reed, G. L., Forbes, A. L., and Roberts, H. R. Calcium, phosphorus, iron, iodine, and zinc in the "total diet." J. Am. Diet Assoc. 77: 16 (1980).
16. Wood, F. O. Present usage of iodized salt in the United States—geographic differences. In: Iodine Nutriture in the United States: Summary of a Conference. Food Nutrition Board, National Academy of Sciences, National Research Council, Washington, D.C., 1970.
17. Pittman, J. A., Dailey, G. F., and Beesh, R. J. Changing normal values for thyroid radioidine uptake. N. Engl. J. Med. 280: 1431 (1969).
18. Bernard, J. D., McDonald, R. A., and Nesmith, J. A. New normal ranges for the radioiodine uptake study. J. Nucl. Med. 11: 449 (1970).
19. Caplan, R. H., and Kujak, R. Thyroid uptake of radioactive iodine, a reevaluation. J. Am. Med. Assoc. 215: 916 (1971).
20. Vought, R. L. Upward trend in iodide consumption in the United States. In: Trace Substances in Environmental Health—V. A. Symposium, D. D. Hemphill, Ed., University of Missouri, Columbia, Mo., 1972, pp. 307-312.
21. Workshop on the Current Exposure to Iodine, sponsored by the Department of Foods and Nutrition, American Medical Association, Scottsdale, Arizona, Nov. 1979.
22. Fisher, K. D., and Carr, C. J. Iodine in foods: chemical methodology and sources of iodine in the human diet. Life Sciences Research Office, Federation of American Scientists for Experimental Biology, Bethesda, Md. PB 233 559, National Technical Information Service, Springfield, Va., 1974.
23. Talbot, J. M., Fisher, K. D., and Carr, J. C. A review of the effects of dietary iodine on certain thyroid disorders.

April 1981
Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md. PB 262 136, National Technical Information Service, Springfield, Va., 1976.

24. Connolly, R. J., Vidor, G. I., and Stewart, J. C. An increase in thyrotoxicosis in an endemic goitre area after iodization of bread. Lancet 1: 500 (1970).

25. Fierro-Beinitez, R., Ramirez, I., Estrella, E., Jaramillo, C., Diaz, C., and Urresta, J. Iodized-oil in prevention of endemic goiter and associated defects in the Andean region of Ecuador. In: Endemic Goiter, PAHO Sci. Pub. No. 193, 1969, p. 306.

26. Matovinovic, J. Complications of goiter prophylaxis. In: Endemic Goiter and Endemic Cretinism, J. B. Stanbury and B. S. Hetzel, Eds., Wiley, New York, 1980, pp. 533-549.

27. Adams, D. D., Kennedy, T. H., Stewart, J. C., Utiger, R. D., and Vidor, G. I. Hyperthyroidism in Tasmania, following iodide supplementation: measurements of thyroid-stimulating antibodies and thyrotropin. J. Clin. Endocrinol. Metab. 41: 221 (1975).

28. Ermans, A. M., and Camus, M. Modification of thyroid function induced by chronic administration of iodide in the presence of “autonomous” thyroid tissue. Acta Endocrinol. 70: 463 (1972).

29. Savoie, J. C., Massin, J. P., Thomopoulos, P., and Leger, F. Iodide-induced thyrotoxicosis in apparently normal thyroid glands. J. Clin. Endocrinol. Metab. 41: 685 (1975).

30. Wolff, J. Iodide goiter and the pharmacologic effects of excess iodide. Am. J. Med. 47: 101 (1969).

31. Carswell, F., Kerr, M. M., and Hutchison, J. H. Congenital goiter and hypothyroidism produced by maternal ingestion of iodides. Lancet 1: 1241 (1970).

32. Barnes, N. D., O'Connell, E. J., and Cloutier, M. D. Iodide-induced (SSKI) hypothyroidism in infancy. Ann. Allergy 35: 306 (1975).

33. Braverman, L. E., Woebier, K. A., and Ingbar, S. H. Induction of myxedema by iodide in patients euthyroid after radiiodine or surgical treatment of diffuse toxic goiter. N. Engl. J. Med. 281: 816 (1969).

34. Braverman, L. E., Ingbar, S. H., Vagenakis, A. G., Adams, L., and Malof, F. Enhanced susceptibility to iodine myxedema in patients with Hashimoto's disease. J. Clin. Endocrinol. Metab. 32: 515 (1971).

35. Suzuki, H., Higuchi, T., Sawa, K., Ohtaki, S., and Horuchi, Y. "Endemic Coast Goitre" in Hokkaido, Japan. Acta Endocrinol. 50: 161-176 (1976).

36. Jubiz, W., Carlile, S., and Lageronist, L. D. Serum thyrotropin and thyroid hormone levels in humans receiving potassium iodide. J. Clin. Endocrinol. Metab. 44: 379 (1977).

37. Azzari, F. Bentley, D., Vagenakis, A., Portnay, G., Bush, J. E., Swachman, H., Ingbar, S. H., and Braverman, L. E. Abnormal thyroid function and response to iodides in patients with cystic fibrosis. Trans. Assoc. Am. Physicians 87: 111 (1974).

38. Braverman, L. E., Vagenakis, A. G., Wang, C., Malof, F., and Ingbar, S. H. Studies on the pathogenesis of iodide myxedema. Trans. Assoc. Am. Physicians 64: 130 (1971).

39. Clark, O. H., Moser, C., Cavaliere, R. R., Hammond, M. E., and Ingbar, S. H. Iodide sensitivity in the hemithyroidecтомized patient. In: Thyroid Research, J. Robbins and L. E. Braverman, Eds. American Elsevier, New York, 1976, pp. 477-480.

40. Hagen, G. A., Ouellette, R. P., and Chapman, E. M. Comparison of high and low dosage levels of 131I in the treatment of thyrotoxicosis. N. Engl. J. Med. 277: 559 (1967).

41. Suzuki, H., and Mashimo, K. Significance of the iodide-perchlorate discharge test in patients with 131I-treated and untreated hyperthyroidism. J. Clin. Endocrinol. Metab. 34: 332 (1972).

42. Vagenakis, A. G., Wang, C., Burger, A., Malof, F., Braverman, L. E., and Ingbar, S. H. Iodide-induced thyrotoxicosis in Boston. N. Engl. J. Med. 257: 523 (1972).

43. Ahmad, M., Doe, R., and Nuttal, F. Q. Triiodothyronine thyrotoxicosis following iodide ingestion: a case report. J. Clin. Endocrinol. Metab. 38: 574 (1974).

44. Blum, M., Weinberg, U., Shoenkman, L., and Hollander, C. S. Hyperthyroidism after iodinated contrast medium. N. Engl. J. Med. 291: 24 (1974).

45. Takeuchi, K., Suzuki, H., Horiiuchi, Y., and Machino, K. Significance of iodine organization defect of the thyroid. J. Clin. Endocrinol. Metab. 31: 144 (1970).

46. Dimitriadou, A., and Fraser, R. Iodide goitre. Proc. Roy. Soc. Med. 54: 345 (1961).

47. Freund, G., Thomas, W. C., Jr., Bird, E. D., Kinman, R. N., and Black, A. P. Effect of iodinated water supplies on thyroid function. J. Clin. Endocrinol. Metab. 26: 619 (1966).

48. Thomas, W. C., Jr., Malagodi, M. H., Oates, T. W., and McCourt, J. P. Effects of an iodinated water supply. Trans. Am. Clin. Climatol. Assoc. 90: 153 (1978).

49. Weaver, D. K., Nishiya, R. H., Burton, W. D., and Batsakis, J. G. Surgical thyroid disease: a survey before and after iodine prophylaxis. Arch. Surg. 92: 796 (1966).

50. Weaver, D. K., Batsakis, J. G., and Nishiya, R. H. Relationship of iodine to lymphocytic goiters. Arch. Surg. 98: 183 (1969).

51. Furszyfer, J., Kurland, L. T., Woolner, L. B., Elveback, L. R., and McConahey, W. M. Hashimoto's thyroiditis in Olmsted County, Minnesota, 1935 through 1967. Mayo Clin. Proc. 45: 886 (1970).

52. Beierwaltes, W. H. Iodine and lymphocytic thyroiditis. Bull. All India Med. Sci. 3: 145 (1969).

53. McCarron, R. Note on experimental production of lymphoadenoid goiter in rats. Brit. Med. J. 1: 5 (1929).

54. Follis, R. H., Jr. Further observations on thyroiditis and colloid accumulation in hyperplastic thyroid glands in hamsters receiving excess iodine. Lab. Invest. 13: 1590 (1964).

55. Evans, T. C., Beierwaltes, W. H., and Nishiyama, R. H. Experimental canine Hashimoto's thyroiditis. Endocrinology 84: 641 (1969).

56. Rallison, M. L., Dobsyn, B. M., Keating, F. R., Rall, J. E., and Tyler, F. H. Thyroid disease in children. A survey of subjects potentially exposed to fallout radiation. Am. J. Med. 56: 457 (1974).

57. Carey, C., Skosy, C., Fismanenani, K. M., Barsano, C. P., and DeGroot, L. J. Thyroid abnormalities in children of parents who have Graves' disease: possible Pre-Graves' disease. Metabolism 29: 269 (1980).

58. Wolff, J., and Chaikoff, J. L. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J. Biol. Chem. 174: 555 (1948).

59. Paris, J., McConahey, W. M., Tauxe, W. N., Woolner, L. B., and Bahn, R. C. The effect of iodides on Hashimoto's thyroiditis. J. Clin. Endocrinol. Metab. 21: 1037 (1961).

60. Wartofsky, L. Low remission rate after therapy for Graves' disease: possible relation of dietary iodine with antithyroid therapy results. J. Am. Med. Assoc. 226: 1083 (1973).

61. Alexander, W. D., Harden, R. M., Koutras, D. A., and Wayne, E. Influence of iodine intake after treatment with antithyroid drugs. Lancet 2: 866 (1965).

62. Thalassinos, N. C., and Fraser, T. R. Effect of potassium
iodide on relapse rate of thyrotoxicosis treated with antithyroid drugs. Lancet 2: 183 (1971).
63. Stanbury, J. B. In: Iodine Nutriture in the United States. Summary of a Conference. Food Nutrition Board, National Academy of Sciences, National Research Council, Washington, D.C., 1970, p. 18.
64. Williams, E. B., Doniach, I., Bjarnsson, O., and Michie, W. Thyroid cancer in an iodine rich area. Cancer 39: 215 (1977).
65. Talbot, J. M., Fisher, K. D., and Carr, C. J. A Review of the Significance of Untoward Reactions to Iodine in Foods. Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md. PB 257 716, National Technical Information Service, Springfield, Va., 1974.
66. Workshop on the Current Exposure to Iodine. Sponsored by the Department of Foods and Nutrition, American Medical Association. Scottsdale, Arizona, Nov. (1979).
Proceedings in preparation.
67. Freeman, M., Giuliani, M., Schwartz, E., and Gomprecht, R. F. Acute thyrotoxicosis, thyroid crisis, and hypocalcemia following radioactive iodine therapy. N. Y. State J. Med. 69: 2036 (1969).
68. Shafer, R. B., and Nuttal F. Q. Thyroid crisis induced by radioactive iodine. J. Nucl. Med. 12: 262 (1971).
69. Maxon, H. R., Thomas, S. R., Saenger, E. L., Bunche, C. R., and Kereiakes, J. G. Ionizing radiation and the induction of clinically significant disease in the human thyroid gland. Am. J. Med. 63: 967 (1977).
70. Schimpff, S. C., Diggs, C. H., Wiswell, J. G., Savastore, P. C., and Wiernik, P. H. Radiation-related thyroid dysfunction: implications for the treatment of Hodgkin's disease. Ann. Intern. Med. 92: 91 (1980).
71. Hammond, E. E., Corrigan, K. E., and Hayden, H. S. Cardiotoxic thyroid and radioactive iodine. J. Am. Med. Assoc. 173: 1902 (1960).
72. Goolden, A. W. G., and Davey, J. B. The ablation of normal thyroid tissue with iodine-131. Brit. J. Radiol. 36: 340 (1963).
73. Fuku, Z., Glatstein, E., Marsa, G. W., Bagshaw, M. A., and Kaplan, H. S. Long-term effects of external radiation on the pituitary and thyroid glands. Cancer 37: 1152 (1976).
74. Hempelmann, L. H. Neoplasms in youthful populations following x-ray treatment in infancy. Environ. Res. 1: 338 W. (1967).
75. Rallison, M. L., Dobyns, B. M., Keating, J. R., Rall, J. E., and Tyler, F. H. Thyroid diseases in children—a survey of subjects potentially exposed to fallout radiation. Am. J. Med. 56: 457 (1974).
76. Raffoff, S., Harrison, J., Karonfls, B. T., Kaplan, E. L., DeGroot, L. J., and Beckerman, C. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N. Engl. J. Med. 292: 171 (1975).
77. Asteris, G. T., and DeGroot, L. J. Thyroid cancer: relationship to radiation exposure and to pregnancy. J. Reprod. Med. 17: 209 (1976).
78. Conard, R. A., DiBlasi, B. M., and Sutow, W. W. Thyroid neoplasia as a late effect of exposure to radioactive iodine in fallout. J. Am. Med. Assoc. 214: 316 (1970).
79. Weiss, E. S., Rallison, M. L., London, W. T., and Thompson, G. D. C. Thyroid nodularity in southwestern Utah schoolchildren exposed to fallout radiation. Am. J. Public Health 61: 241 (1971).
80. Rallison, M. L., Dobyns, B. M., Keating, F. R., Rall, J. E., and Tyler, F. H. Thyroid nodularity in children. J. Am. Med. Assoc. 232: 1069 (1975).
81. Parker, L. N., Belsky, J. L., Yamamoto, T., Kawamoto, S., and Kehrn, R. J. Thyroid carcinoma after exposure to atomic radiation: a continuing survey of a fixed population. Ann. Intern. Med. 80: 600 (1974).
82. Socolow, E. L., Hashizume, A., Neriishi, S., and Niitani, R. Thyroid carcinoma in man after exposure to ionizing radiation. A summary of the findings in Hiroshima and Nagasaki. N. Engl. J. Med. 268: 406 (1963).
83. Population Dose and Health Impact of the Accident at the Three Mile Island Nuclear Station. Ad Hoc Population Dose Assessment Group. May, 1979, Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. Stock No. 017-001-00408-1.
84. Freedberg, A. S., Kurland, G. S., and Blumgart, H. L. The pathological effects of I-131 on the normal thyroid gland of man. J. Clin. Endocrinol. Metab. 12: 1315 (1952).
85. Holm, L.-E., Dahlqvist, I., Israelsson, A., and Lundell, G. Malignant thyroid tumors after iodine-131 therapy. A retrospective cohort study. N. Engl. J. Med. 303: 188 (1980).
86. Beach, S. A., and Dolphin, G. W. A study of the relationship between x-ray dose delivered to the thyroids of children and the subsequent development of malignant tumors. Phys. Med. Biol. 6: 583 (1962).
87. Hanford, J. M., Quimby, E. H., and Frantz, V. K. Cancer arising many years after radiation therapy: incidence after irradiation of benign lesions in the neck. J. Am. Med. Assoc. 181: 404 (1962).
88. DeLawter, D. S., and Winship, T. Follow-up study of adults treated with roentgen rays for thyroid disease. Cancer 16: 1028 (1963).
89. Markson, J. L., and Flattman, G. E. Myxoedema after deep x-ray therapy to the neck. Brit. Med. J. 1: 1228 (1963).
90. Dobyns, B. M., Sheline, G. E., Workman, J. B., Tompkins, E. A., McConahey, W. M., and Becker, D. V. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy followup study. J. Clin. Endocrinol. Metab. 38: 976 (1974).
91. Safa, A. M., Schumacher, O. P., and Rodríguez-Antunez, A. Long-term follow-up results in children and adolescents treated with radioactive iodine (I-131) for hyperthyroidism. N. Engl. J. Med. 292: 167 (1975).
92. Foster, R. S., Jr. Thyroid irradiation and carcinogenesis. Review with assessment of clinical implications. Am. J. Surg. 130: 606 (1975).
93. Pfliech, B. Z., Kain, C. R., Ketcham, A. S., and Henson, D. Thyroid cancer after radioactive iodine diagnostic procedures in childhood. Pediatrics 51: 898 (1973).
94. Weshler, Z., Krasnokuki, D., Peshin, Y., and Biran, S. Thyroid carcinoma induced by irradiation for Hodgkin's disease: report of a case. Acta Radiol. Oncol. Radiat. Phys. Biol. 17: 383 (1978).
95. Fuku, Z., Glatstein, E., Marsa, G. W., Bagshaw, M. A., and Kaplan, H. S. Long-term effects of external radiation on the pituitary and thyroid glands. Cancer (Suppl. 2) 37: 1182 (1976).
96. Frank, H. J. L., and Ashcraft, M. W. Thyroid carcinoma after radiation for Hodgkin's disease. Ann. Intern. Med. 92: 145 (1980).
97. Hempelmann, L. H., Hall, W. J., Phillips, M., Cooper, R. A., and Ames, W. R. Neoplasms in persons treated with x-ray in infancy: fourth survey in 20 years. J. Natl. Cancer Inst. 55: 519 (1975).
98. Chase, L., Mattar, A., Phillips, G., Dreixel, A., and Askin, F. A functioning thyroid nodule in a patient previously treated with irradiation for Hodgkin's disease. Am. J. Med. 68: 429 (1980).
99. Getaz, E. P., and Shimaoka, K. Anaplastic carcinoma of the thyroid in a population irradiated for Hodgkin's dis-
100. Duffy, B. J., Jr., and Fitzgerald, P. J. Cancer of the thyroid in children: a report of 28 cases. J. Clin. Endocrinol. Metab. 10: 1296 (1950).

101. Clark, D. E. Association of irradiation with cancer of the thyroid in children and adolescents. J. Am. Med. Assoc. 159: 1007 (1956).

102. Hempelmann, L. H. In: Thyroid Neoplasia. S. Young and D. R. Inman, Eds., Academic Press, New York-London, 1968, p. 267.

103. Favus, M. J., Schneider, A. B., Stachura, M. E., Arnold, J. E., Ryo, U. Y., Pinsky, S. M., Colman, M., Arnold, M. J., and Frohman, L. A. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. N. Engl. J. Med. 294: 1019 (1976).

104. Cerletty, J. M., Guansing, A. R., Enbring, N. H., Hagen, T. C., Kim, H. J., Shetty, K. R., Wilson, S., and Rosenfeld, P. S. In: Radiation Associated Thyroid Carcinoma. L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. Refetoff, Eds., Grune and Stratton, New York, 1977, pp. 1-3.

105. Carroll, R. G., Ellis, L. D., Moore, D., Gaudio, A., Youngquist, C. R., Robinnette, J., Stark, N., Heinz, E. R., Girdany, B. R., Myers, E., and Schramm, V. Organization of screening program for detection of thyroid cancer. In: Radiation Associated Thyroid Carcinoma. L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. Refetoff, Eds., Grune and Stratton, New York, 1977, pp. 271-280.

106. DiGuilio, W., Douglas, R., Fink-Benner, D., Levine, A., and Miller, J. M. Results of screening patients with prior irradiation to the head and neck in 5 Detroit area hospitals. In: Radiation Associated Thyroid Carcinoma. L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. Refetoff, Eds., Grune and Stratton, New York, pp. 33-34.

107. Hempelmann, L. H. Risk of thyroid neoplasms after irradiation in childhood. Science 160: 159 (1968).

108. Goodden, A. W. G. Carcinoma of the thyroid following radiation. Brit. Med. J. 2: 954 (1968).

109. Raventos, A., and Winship, T. The latent interval for thyroid cancer following irradiation. Radiology 88: 501 (1964).

110. Schneider, A. B., Favus, M. J., Stachura, M. E., Arnold, J., Arnold, M. J., and Frohman, L. A. Incidence, prevalence and characteristics of radiation-induced thyroid tumors. Am. J. Med. 64: 243 (1978).

111. Doniach, I. Experimental induction of tumors of the thyroid by radiation. Brit. Med. Bull. 14: 181 (1958).

112. Beierwaltes, W. H., Crane, H. R., Wegst, A., Spafford, N. R., and Carr, E. A. Radioactive iodine concentration in the fetal human thyroid gland from fall-out. J. Am. Med. Assoc. 173: 1850 (1960).

113. McDougall, I. R., and Grieg, W. R. I31 therapy in Graves’ disease. Long-term results in 355 patients. Ann. Intern. Med. 85: 720 (1976).

114. Kouts, H. Physical aspects of reactor accidents. Address to 62nd Annual Meeting of the Endocrine Society, Washington, D.C., June 1980.

115. Nisbet, I. C. T., and Serafin, A. F. Rates and routes of transport of PCB's in the environment. Environ. Health Perspect. 1: 21 (1972).

116. Proceedings of the Conference on PCB's. Rougemont, North Carolina, December 1971. Environ. Health Perspect. 1: 1 (1972).

117. Conference Proceedings, National Conference on Polychlorinated Biphenyls. Chicago, Ill., November, 1975. J. L. Buckley, Ed., Environmental Protection Agency, Washington, D.C., Publication No. EPA-560/6-75-004, 1976, pp. 1-471.

118. Kimbrough, R. D. The toxicity of polychlorinated polycyclic compounds and related chemicals. Crit. Rev. Toxicol. 2: 445 (1974).

119. Matovinovic, J., and Trowbridge, F. L. Effect on polychlorinated biphenyls on the thyroid gland in animals. In: Endemic Goiter and Endemic Cretinism, J. B. Stanbury and B. S. Hetzel, Eds., Wiley, New York, 1980, pp. 56-61.

120. Black, J. J., and Simpson, C. L. Thyroid enlargement in Lake Erie Coho salmon. J. Natl. Cancer Inst. 53: 725 (1974).

121. Sonstegard, R., and Leatherland, J. F. The epizootiology and pathogenesis of thyroid hyperplasia in Coho salmon (Onchorhyncus kisutch) in Lake Ontario. Cancer Res 36: 4467 (1976).

122. Moccia, R. D., Leatherland, J. F., and Sonstegard, R. A. Increasing frequency of thyroid goiters in Coho salmon (Onchorhyncus kisutch) in the Great Lakes. Science 198: 425 (1977).

123. Stalling D. L., and Mayer, F. L., Jr. Toxicities of PCB's to fish and environmental residues. Environ. Health Perspect. 21: 159 (1972).

124. Robertson, O. H., and Chaney, A. L. Thyroid hyperplasia and tissue iodine content in spawning rainbow trout: a comparative study of Lake Michigan and California sea-run trout. Physiol. Zool. 26: 328 (1953).

125. Bastomsky, C. H., Murthy, P. V. N., and Banovac, D. Alterations in thyroid hormone metabolism produced by cutaneous application of microsize immersion oil: effects due to polychlorinated biphenyls. Endocrinology 98: 1309 (1976).

126. Bastomsky, C. H. Goiters in rats fed polychlorinated biphenyls. Can. J. Physiol. Pharmacol. 55: 288 (1977).

127. Allen-Rowlands, C., Castracane, V. D., and Seifert, J. Effects of polybrominated biphenyls (PBB's) on thyroid, adrenal, and testes function in the rat. Paper presented at 61st Annual Meeting of the Endocrine Society, Anaheim, California, June 1979.

128. Kuratsune, M., Masuda, Y., and Nagayama, J. Some of the recent findings concerning Yusho. In: Conference Proceedings, National Conference on Polychlorinated Biphenyls. J. L. Buckley, Ed., Environmental Protection Agency, Washington, D.C., Publication No. EPA-560/6-75-004, 1976.

129. Kuratsune, M., Yoshimura, T., Matsuoka, J., and Yamaguchi, A. Epidemiologic study of Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyl. Environ. Health Perspect. 1: 119 (1972).

130. Price, H. A., and Welch, R. L. Occurrence of polychlorinated biphenyls in humans. Environ. Health Perspect. 1: 73 (1972).

131. Yobs, A. R. Levels of polychlorinated biphenyls in adipose tissue of the general population of the nation. Environ. Health Perspect. 1: 79 (1972).

132. Bahn, A. K., Mills, J. L., Snyder, P. J., Gann, P. H., Houten, L., Bialik, O., Hollmann, L., and Utiger, R. D. Hypothyroidism in workers exposed to polybrominated biphenyls. N. Engl. J. Med. 302: 31 (1980).

133. Stross, J. K. Hypothyroidism and polybrominated biphenyls. N. Engl. J. Med. 302: 1421 (1980).