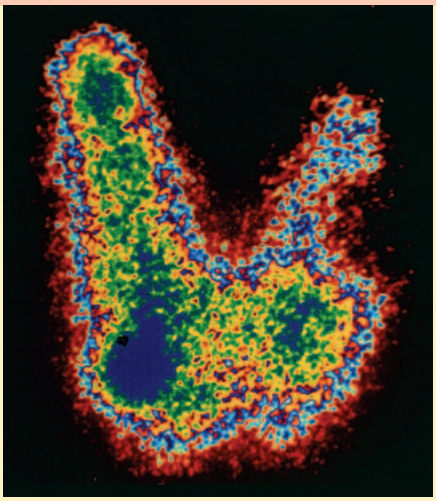
Disrupting a Delicate Balance

Environmental Effects on the Thyroid



Public and scientific unease about possible disruption of hormones by man-made substances in the environment has gathered steam steadily over the last decade, propelled significantly by two events of 1996: the publication of *Our Stolen Future*, by Theo Colborn, Dianne Dumanoski, and John Peterson Myers, and the passage by Congress of the Food Quality Protection Act and amendments to the Safe Drinking Water Act, directing the U.S. Environmental Protection Agency (EPA) to determine whether and to what extent industrial chemicals disrupt reproductive and thyroid hormones.

In response to its congressional mandate, the EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). In its 1998 final report, EDSTAC recommended that the EPA address the effects of pesticides, commercial chemicals, and other environmental contaminants on the endocrine system, which comprises the body's hormones and glands—the pituitary gland, the adrenal gland, the ovaries, the testes, the pancreas, the hypothalamus, the parathyroid gland, and the thyroid gland.

Because the thyroid affects the adult body's major systems, and because it is crucial to fetal development, its disruption by exogenous chemicals is of intense interest. Moreover, the thyroid, along with breast tissue and bone marrow, is especially vulnerable to ionizing radiation. Taken together, these aspects of the thyroid make understanding environmental influences on it a fascinating puzzle requiring a multidisciplinary meld of endocrinology, toxicology, and nuclear medicine to untangle.

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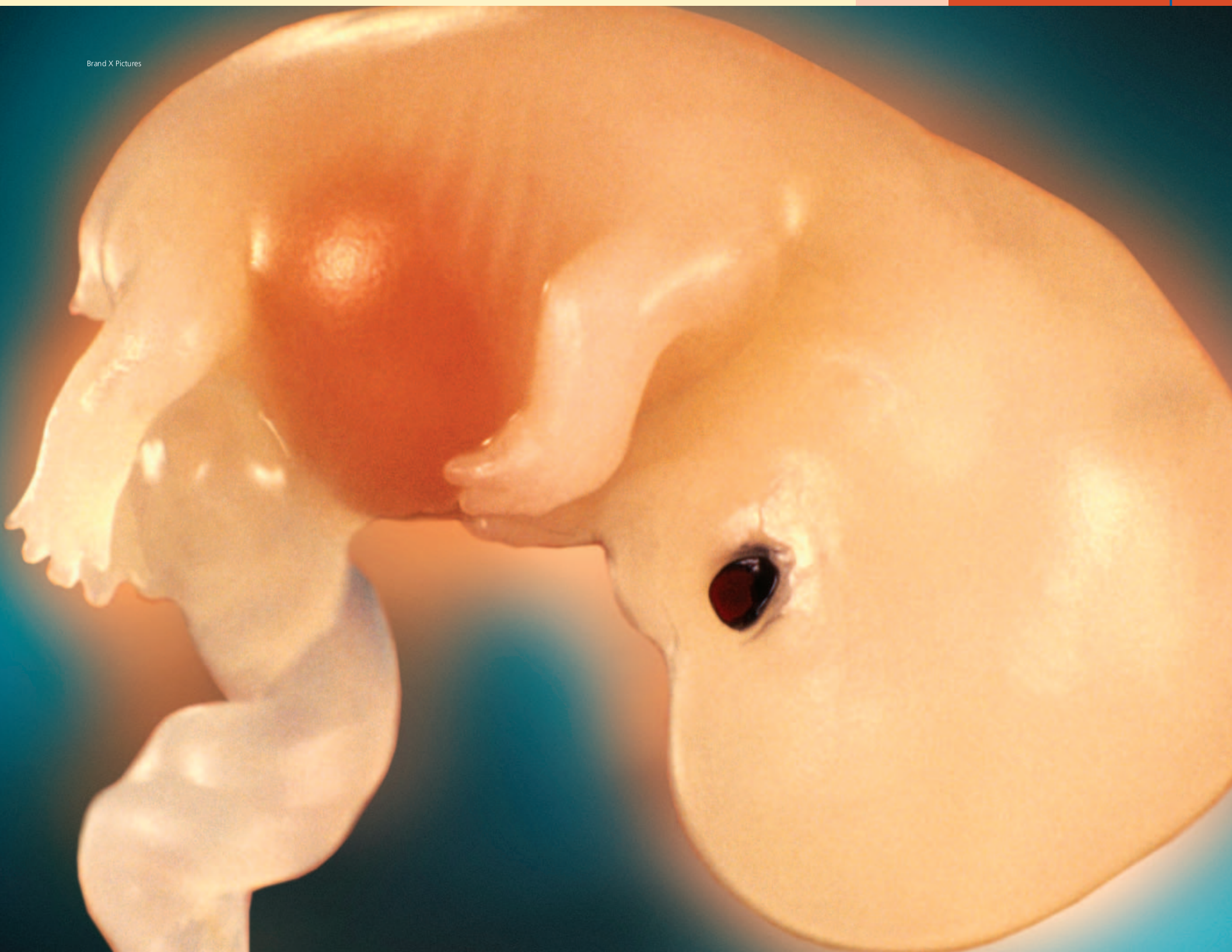
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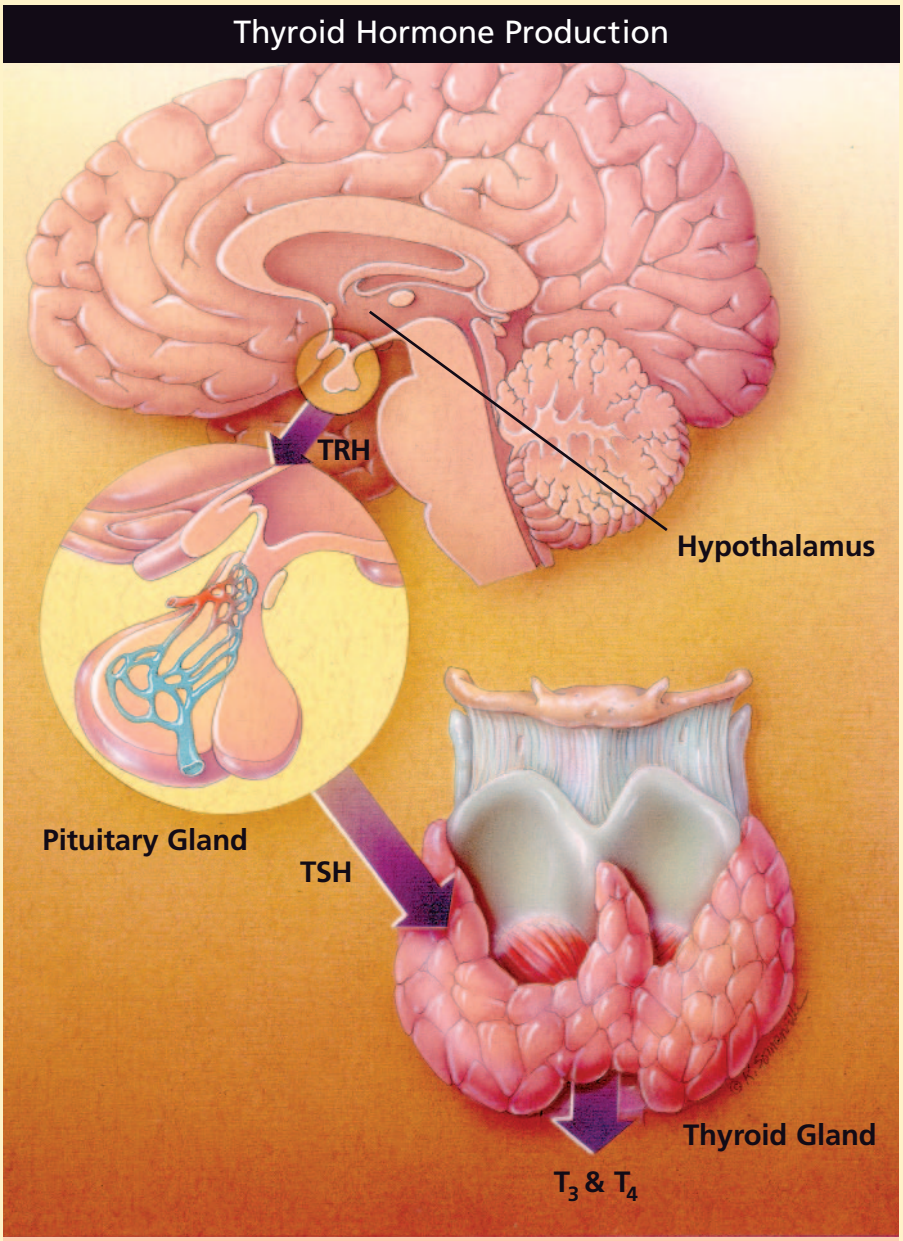


An elegant system. The thyroid regulates its hormone output with the aid of the hypothalamus and the pituitary gland. The hypothalamus secretes thyrotropin-releasing hormone (TRH), triggering the pituitary to make thyroid-stimulating hormone (TSH). TSH tells the thyroid to capture iodine from the blood to synthesize, store, and release thyroxine (T_4). When T_4 reaches target cells, it is converted to triiodothyronine (T_3). The hypothalamus and pituitary reduce their output of TRH and TSH once T_4 reaches an adequate circulating level, then resume output when the T_4 level again drops.

Thyroid Basics

The butterfly-shaped thyroid gland, sitting at the base of the neck just below the larynx, influences basic metabolism, heart rate, blood pressure, and body temperature, among other functions. A variety of disorders can plague it, including autoimmune disorders, benign and malignant tumors, and goiter (an enlargement of the thyroid that may be caused by either over- or underproduction of thyroid hormone). About 13 million Americans have thyroid disorders, of which nearly 11 million are women and more than half are undiagnosed, according to the Thyroid Foundation of America.

Iodine is required to make the thyroid's two principal products—thyroxine (T_4) and triiodothyronine (T_3), generally known collectively as "thyroid hormone." The World Health Organization (WHO) estimates that 740 million people worldwide suffer from iodine deficiency—the most common cause of preventable thyroid disease and mental retardation in the world—and only about 57% of people in the developing world consume iodized salt, the primary means of correcting iodine deficiency. Iodine deficiency is common in inland areas of the world where people do not have access to iodine-rich foods such as ocean fish, kelp, and sea salt, or where they consume foods that interfere with the body's uptake of iodine.

Iodine deficiency results in hypothyroidism, which leads to weight gain, fatigue, dry skin, mood swings, and goiter, among other symptoms. Excess hormone production, or hyperthyroidism, can cause anxiety, heart palpitations, insomnia, hair loss, and weight loss, as well as goiter.

The thyroid is elegantly self-regulating, enlisting the support of the hypothalamus and the pituitary gland to maintain a steady state of hormone availability to the body. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which tells the pituitary to make thyroid-stimulating hormone (TSH). TSH tells the thyroid gland itself to capture iodine from the blood to synthesize, store, and release T_4. Once T_4 has reached an adequate circulating level, the hypothalamus and pituitary reduce their output of TRH and TSH until the T_4 level again drops. T_4 circulates in the blood both freely and bound to carrier proteins. When T_4 reaches target cells, it is converted to T_3, which is the biologically active form. (T_3 also can be released by the thyroid and can bind to carrier proteins.)

A Difficult Subject

The study of the thyroid and its products presents special challenges to researchers. Thyroid hormones differ markedly from reproductive hormones in several respects, and these differences have made it difficult to transfer the reproductive hormone model of chemical endocrine disruption to the thyroid system. For one thing, estrogens and androgens are released into the body in what endocrinologist R. Thomas Zoeller of the University of Massachusetts Amherst, who was a member of EDSTAC, calls a "regulatory pulse." In contrast, thyroid product levels "stay pretty much the same all the time," and if disturbed will attempt to return to normal levels. Further, the thyroid system affects bodily processes more globally and more subtly than reproductive hormones. Thyroid products are "necessary but not sufficient" to affect physiological processes, says Zoeller; they are likely to work in concert with other hormones or vitamins rather than independently.

Whereas much of the early endocrine disruption research started with the effects of chemicals on nuclear receptors, research into thyroid disruption initially concentrated on

Kevin Somerville

trying to determine whether chemicals affect circulating levels of TSH and T_4. But measuring TSH and T_4 is a relatively uncertain assay for detecting the effects of low-level or chronic chemical or radiation exposure. Assays for serum hormones including T_3, T_4, and TSH are fairly sophisticated, says Zoeller, "but measuring hormone levels as an assay of thyroid disruption does not tell us whether there are adverse effects of this disruption."

For example, he explains, scientists are finding that very subtle reductions in circulating T_4—reductions so subtle that they can't be measured directly but can only be deduced from a small increase in TSH—can cause a change in specific developmental processes in the brain that are controlled by thyroid hormone. Thus, he says, the typical interpretation of this observation would be that the increase in TSH was compensatory because there were no end points incorporated into the experimental design to track the effects of these changes. This uncertainty has made it more difficult for researchers to identify possible changes in thyroid function and metabolism that may not be reflected in circulating hormone levels.

With regard to reproductive hormones, "It's [relatively] easy to pick out measurements that will provide some degree of specificity of effect—if you see the effect, you can be reasonably sure that the compound was an estrogen or androgen," says developmental toxicologist George Daston, a research fellow at Procter & Gamble in Cincinnati who served on EDSTAC. "With the thyroid, we're having a lot of difficulty pinning down that degree of specificity." For example, the markers of congenital hypothyroidism, such as small stature, low birth weight, and vision and motor problems, can be caused by factors other than developmental thyroid disruption.

Thyroid and Brain Development

Although it is important to understand how environmental exposures may affect adults, effects in adults may be less significant as the thyroid's self-correcting feedback system helps the adult body right itself, and if this fails, hormone supplementation usually reestablishes balance. However, the developing fetus depends upon maternal thyroid hormones until around the beginning of the second trimester, and at no time is thyroid hormone more crucial than during brain development. Thus, it is in fetal and childhood development that environmental factors may have their greatest impact.

Some neurodevelopmental problems, such as extreme mental retardation and deaf-mutism, can be prevented or at least mitigated with postnatal hormone treatment. But even with treatment, children of hypothyroidal mothers have a higher-than-normal incidence of difficulties with spatial, perception, memory, language, and other skills. In a review of thyroid and brain development in the June 1994 issue of *EHP Supplements*, Susan Porterfield, an endocrinologist at the Medical College of Georgia in Augusta, suggested that these problems probably stem more from the fetus's lack of available thyroid hormone than from inadequate hormone replacement for the newborn. Therefore, because most developmental deficits are irreversible, mechanisms by which environmental exposures disrupt the thyroid's role in development are currently the focus of much research interest.

Basic fetal brain development is under way in humans within the first few weeks of gestation. Spinal cord and hindbrain components grow at this point, and cerebral cortex structures begin to take shape about halfway through gestation. Neural synapses begin forming as early as the second month of gestation, peaking in the child's first year of life, and many parts of the brain continue to develop postnatally and even into adulthood. Thyroid hormone is essential for neuron formation, synapse development, formation of myelin (the sheath surrounding neurons that enhances nerve impulse transmission), and migration of neurons to their proper places in the brain.

Although the fetal thyroid begins to grow around the end of the first trimester, it does not begin producing its own products until the second trimester, and the hypothalamic–pituitary–thyroid axis is not mature until the last trimester. Thus, maternal thyroid hormone must be continuously available until birth because crucial brain development take place before the fetus's thyroid system is up and running.

Extreme maternal hypothyroidism leads to neurological cretinism, which can include spastic diplegia (a form of cerebral palsy), deafness, and severe mental retardation. On the other hand, maternal hyperthyroidism can result in low birth weight, prematurity, and, in the case of maternal Graves disease (an autoimmune disorder marked by hyperthyroidism), an increased incidence of congenital malformations.

Even small changes in thyroid hormone availability during critical periods of brain development can have troubling results. Children born to mothers with hypothyroxinemia, or low circulating levels of T_4, may have difficulty with motor coordination, balance, and other psychomotor problems. Some research also suggests that attention deficit/hyperactivity disorder may result in children of hypothyroidal mothers, and studies summarized by Gabriella Morreale de Escobar and colleagues from Madrid's Alberto Sols Biomedical Research Institute in the November 2000 issue of the *Journal of Clinical Endocrinology & Metabolism* demonstrate 5- to 6-point IQ deficits in children of mothers with hypothyroxinemia.

For these reasons, elucidating the effects of low-level exposures to environmental toxicants during gestation is vital, says Ted Schettler, science director for the Science and Environmental Health Network, a nongovernmental organization. Schettler, who served on EDSTAC, points out that even small changes in IQ resulting from fetal thyroid hormone disruption can have important ramifications, depending on where the person falls on the IQ spectrum. A drop in IQ from 75 to 70, for example, can make the difference between institutional care and independent living, which in turn translates to significant economic effects on society.

Answering the questions regarding environmental factors in fetal brain development involving the thyroid would be easier if there were only one or two mechanisms by which thyroid function can be disrupted. But in a comprehensive September 1998 review article in *Thyroid*, Françoise Brucker-Davis, now on the faculty at the Centre Hospitalier Universitaire in Nice, France, identified nearly 90 separate compounds having thyroid-disrupting properties. And in the June 2002 issue of *EHP Supplements*, Kembra L. Howdeshell, now a postdoctoral fellow working at the University of Michigan in Ann Arbor, noted 12 separate types of interference in thyroid mechanisms. This recent work builds on earlier research and analysis by scientists such as Charles Capen, a professor of veterinary biosciences at The Ohio State University in Columbus, and R. Michael McClain, formerly a research leader at Hoffman-La Roche, who in the 1980s first espoused the idea that there are multiple mechanisms by which environmental agents alter thyroid function.

The primary types of interference in thyroid mechanisms are inhibition of iodine uptake by the thyroid gland, binding of exogenous chemicals to the serum proteins normally intended to transport T_4 to target cells, inhibition of hormone synthesis in the gland, and breakdown and elimination of thyroid products by the liver. There is also the possibility that some chemicals interfere with cellular utilization of thyroid hormone by attaching to the receptors and acting as agonists or

antagonists of the hormone action itself, or by interacting with receptor cofactors. Research has not yet clearly established these processes, however.

Chemical Culprits?

In her 1998 review of both animal and human studies, Brucker-Davis found that, in general, there was abundant evidence from wildlife and laboratory animal research that environmental chemicals do disrupt thyroid function. Yet she could come to few firm conclusions with respect to humans, partly because many human studies indicate only mild effects, and, she wrote, because "the presence of multiple contaminants makes it difficult to sort out the respective role of individual chemicals."

Brucker-Davis argued in her review that the strongest evidence of thyroid disruption by chemicals is that iodine deficiency occurs in iodine-sufficient areas, implying that some unidentified influence interrupts what would otherwise be a fairly straightforward process. As a research agenda, she suggested concentrating on the chemicals having structures similar to thyroid hormone and those that alter liver metabolism of thyroid hormone. The former are candidates for action at cell receptor sites and binding to carrier proteins, and the latter could trigger the TSH feedback mechanism.

Many of the same chemicals thought to damage the reproductive hormone system are also suspected or known to affect the thyroid. These include polychlorinated biphenyls (PCBs) and their relatives the polybrominated diphenyl ethers (PBDEs), ethylenebisdithiocarbamates (EBDCs), dioxins, and perchlorate. Each family of compounds may contain several different congeners that have similar but not identical actions—or very dissimilar actions, or no actions at all—further complicating the puzzle.

Cancer cloud? Fallout from detonations at the Nevada Proving Grounds (above) and other sites has been the subject of intense research on ionizing radiation, the only known cause of human thyroid cancer.

PCBs, once used widely in electrical equipment, were banned in the United States in 1979 because they were associated with cognitive impairments, immune disorders, and cancer in humans. PBDEs have come into widespread use over the last 20 years as flame retardants in products such as carpet and computer plastics. Both groups are persistent in the environment and bioaccumulate up the food web. Dioxins—by-products of organochlorine synthesis, waste combustion, and paper production—are structurally similar to PCBs and PBDEs. They, too, are persistent and are often mixed with PCBs in the environment.

PCBs probably affect thyroid function by displacing T_4 from serum-binding proteins in blood and by increasing liver metabolism of thyroid hormones. A paradox of PCB effects, says Zoeller, is that they reduce circulating T_4 without increasing TSH. PBDEs and dioxins have similar effects.

EBDCs are potent fungicides. They are used on many plants, including root and leafy vegetables, fruits, and cereals, both in the field and after harvest. They have been known since the 1960s to cause goiter and to inhibit iodine uptake. The body breaks them down to ethylenethiourea, which has been identified by the EPA as a thyroid carcinogen in rats and mice and a probable human carcinogen. EBDCs can lower levels of thyroid hormone in rats at low doses, and may affect TSH. Ethylenethiourea also inhibits thyroid peroxidase, an enzyme necessary for synthesis of T_3 and T_4.

Perchlorate, used as an oxygen source in missile and rocket fuel, is common in drinking water in the southwestern United States. It inhibits iodine uptake by the thyroid, which can result in hypothyroidism and thyroid tumors. The EPA is in the process of setting a reference dose for perchlorate exposure in humans.

But these toxicants aren't the only chemicals that affect the thyroid. Fluoride, an element common in U.S. drinking water either naturally or added as a dental caries preventive, also suppresses thyroid hormone, although the mechanism is not understood, according to Paul Connett, a professor of chemistry at St. Lawrence

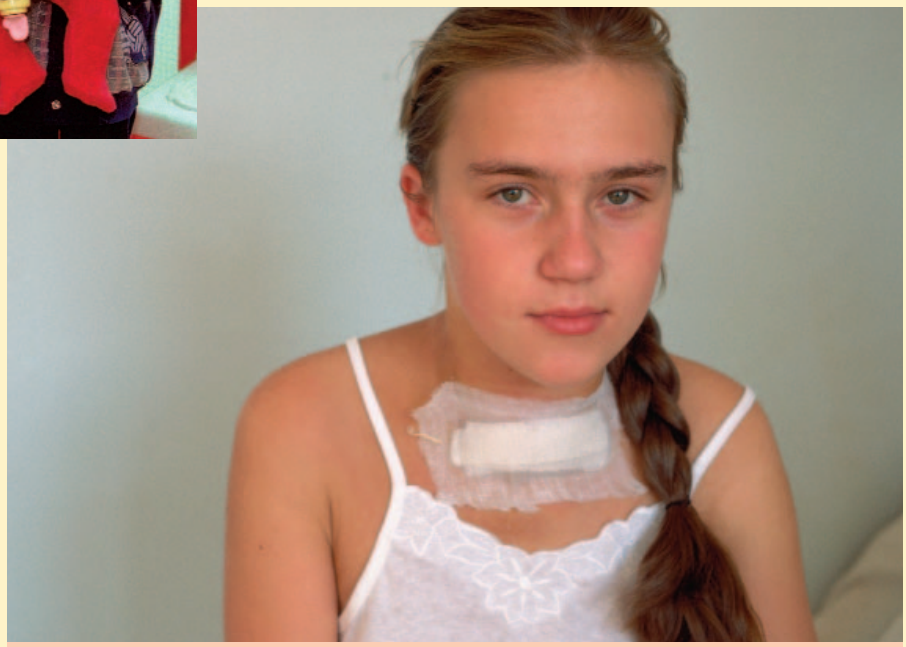
U.S. Department of Energy, Nevada Operations Office

University in Canton, New York, and an activist opposing the addition of fluoride to water. But the U.S. Food and Drug Administration emphasizes that fluoride concentrations in drinking water are safe, and most thyroid researchers believe many other chemicals pose a greater threat.

Another culprit, cyanide, occurs naturally in more than 1,000 plants, including cassava, sorghum, and bamboo, all important food sources in many parts of the developing world. At chronic subacute levels of exposure, cyanide can produce goiter and hypothyroidism. According to the Cassava Cyanide Diseases Network, a collaborative group of government officials and academics in Mozambique and Australia, cyanide contributes to goiter when the diet is already iodine-deficient. Traditional methods of processing cassava effectively neutralize cyanide's health effects, but according to WHO regional surveys of iodine deficiency status in Africa, ongoing wars, famines, and resulting mass migrations of African peoples dependent on cassava have interrupted such processing methods in many places, increasing the exposure of these already-stressed populations.

Soy isoflavones, touted by many as a benign substitute for endogenous estrogens for postmenopausal women, can be goitrogenic, although the amounts usually consumed by adults are insufficient to have that effect. Findings by toxicologist Daniel Doerge of the National Center for Toxicological Research and colleague Daniel M. Sheehan, reported in the June 2002 issue of *EHP Supplements*, suggest that soy isoflavones' ability to disrupt the thyroid depends on other factors such as iodine deficiency, other dietary goitrogens, and underlying thyroid dysfunction. Doergeemphasized the need for further research into the safety of soy isoflavones.

Many other foods contain thyroid-disrupting compounds, such as millet (containing epigenin and luteolin) and the cabbage family (containing goitrin). In parts of Africa where goiter is endemic, such as Sudan and the Republic of Guinea, it probably results from the combination of underlying iodine deficiency and large amounts of millet in the diet.



Far-flung effects. The 1986 explosion and fire at the Chernobyl nuclear power plant exposed some 5 million people in Belarus, Ukraine, and Russia to radioactive fallout. Children are the accident's youngest victims, suffering high rates of thyroid cancers.

Radiation: Out, In, High, Low?

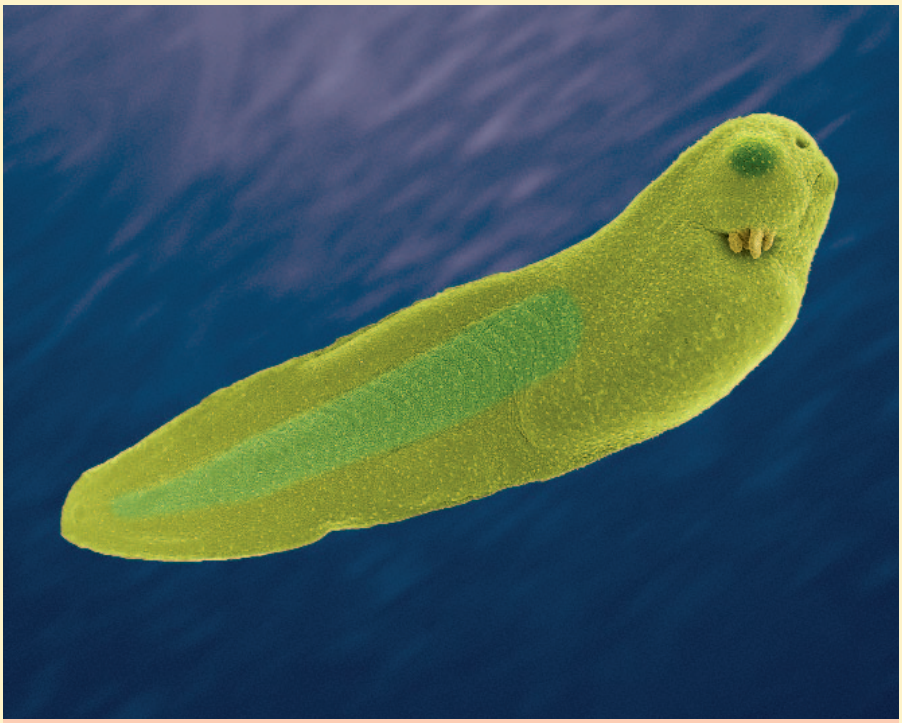
The thyroid can be affected by ionizing radiation through the skin by gamma radiation, including X rays; by fission products, such as cesium; or by ingestion or inhalation of iodine-131 (^{131}I), an isotope present in nuclear fission products. ^{131}I emits mostly beta radiation, which penetrates surfaces more shallowly than gamma radiation. It has a half-life of only about eight days, but in fallout form it can be inhaled directly or taken up by plants eaten by cows and goats, in whose milk it is then expressed. The thyroid cannot distinguish ^{131}I from the nonradioactive form.

Ionizing radiation is at present the only known cause of human thyroid cancer. Thyroid tumors, or nodules, rarely result in detectable disruption of thyroid function. About 1% of these tumors are malignant and are treated with surgery, radiation, or both.

Most radiation research has focused on exposures from nuclear bomb tests, wartime bomb drops, and nuclear power plant accidents. Bomb drops and tests occurred from 1945 until aboveground testing was phased out in 1963. Possibly the most famous nuclear events were the Hiroshima and Nagasaki bombings in 1945. Other significant exposures occurred as the result of weapons production and testing in the Marshall Islands from 1946 to 1958, in the American West north and east of the Nevada bomb tests—principally in Utah and Idaho—from 1951 to 1963, and near the Hanford Nuclear Site in eastern Washington State from 1944 to 1957 (lesser releases continued at Hanford until 1972). The 1986 explosion and fire at the Chernobyl nuclear power plant exposed some 5 million people in Belarus, Ukraine, and Russia to radiation.

Of the fallout victims studied, the Japanese victims received high doses of mixed external radiation in a very short time, the Marshall Islanders and Utah residents received primarily ^{131}I exposure periodically over about 12 years, and Hanford downwinders probably received relatively lower doses, primarily of ^{131}I, from multiple releases over a slightly longer period. The Chernobyl accident produced an acute, rapid exposure, mostly to ^{131}I but also to a mixture of other fission products.

Top to bottom: Caroline Penn/Corbis; AFP/Corbis



***Xenopus* and us.** Researchers are working to develop animal models of gene regulation by thyroid hormone including one that studies the metamorphosis from tadpole (above) to frog of the African clawed frog (*Xenopus laevis*).

Thus, in none of these events was there a clear-cut relationship among radiation type, duration of exposure, and internal versus external exposure.

High doses of external gamma radiation can damage thyroid gland tissue and lead to hypothyroidism as well as benign or malignant nodules, but the effects of low doses, especially of beta radiation such as ^{131}I, are less certain. There was some increase in the incidence of both benign and malignant nodules among weapons-exposed populations, and Chernobyl victims, primarily children, suffered a striking spike in thyroid cancer incidence. According to the United Nations Scientific Committee on the Effects of Atomic Radiation's 2000 report, *Sources and Effects of Ionizing Radiation*, 1,791 children under 18 at the time of the accident were diagnosed with thyroid cancer between 1990 and 1998 in Belarus, Russia, and Ukraine, representing a fourfold increase in incidence. In Belarus, the incidence in children under 15 at diagnosis jumped from 0.2 per 100,000 to 5.6 per 100,000 in 1995, then tapered to 3.9 per 100,000 by 1998. Because some Chernobyl victims were iodine-deficient, their risk of cancer may have been magnified.

Although Chernobyl provided strong evidence that high ^{131}I exposure increases cancer risk, it did not answer the question of whether low chronic doses do so, but research on Hanford downwinders seems to indicate low risk from low chronic doses. Yet, "nothing's crystal-clear regarding radiation effects," says Scott Davis, chairman of the Department of Epidemiology at the University of Washington School of Public Health and Community Medicine in Seattle.

Davis directed the Hanford Thyroid Disease Study (HTDS), which was conducted in response to a 1988 congressional mandate to the U.S. Centers for Disease Control and Prevention (CDC). The study asked whether exposure to ^{131}I from Hanford resulted in increased incidence of thyroid disease among 3,441 subjects identified as having lived in the highest-exposure areas during the relevant period. The study found that the risk of thyroid disease did not vary with radiation dose and that Hanford downwinders were at no higher risk of thyroid disease than the general population. The preliminary HTDS results were released by the CDC in its 1999 *Hanford Thyroid Disease Study Draft Final Report* to a chorus of criticism from downwinders, antinuclear activists, and some scientists. The final CDC report was issued in 2002, but the HTDS results have not yet been published in a peer-reviewed journal; papers based on HTDS data are currently under review by several journals, according to Davis.

The 2000 National Academy of Sciences *Review of the Hanford Thyroid Disease Study Draft Final Report* supported the study's methodology but noted the report's reliance on highly uncertain dose amounts. In addition, Keith Baverstock, a prominent Chernobyl researcher with the WHO European Center for Environment and Health in Bonn, Germany, noted in a comment posted at the HTDS website (**http://www.cdc.gov/nceh/radiation/hanford/htdsweb/index.htm**) that the results could indicate an excess of thyroid cancer cases, and that "there are certainly more cases detected than would be expected on the basis of the national rates for invasive thyroid cancer." Follow-up research on the Hanford and Chernobyl victims is ongoing.

Next Steps

At this point in the understanding of environmental effects on the thyroid, there are far more questions than answers, but whether the toxicant under consideration is chemical or radioactive, most of the questions have to do with the effects of low-level exposures rather than acute ones. A further critical issue is whether combinations of toxicants have synergistic effects or sometimes even cancel each other out. Because the effects of low-level exposure may be subtle, Schettler thinks the precautionary principle should be implemented long before unambiguous results accumulate from laborious laboratory and epidemiologic studies.

As researchers implement the EPA mandate to study endocrine disruption, they must tackle some difficult procedural issues. For example, the rat thyroid system has been well characterized, but because rats and humans may metabolize certain toxicants differently (and thus, for example, rats may receive noncomparable doses of hydrophobic toxicants such as PCBs via breast milk), it is not certain how confidently researchers can extrapolate rat results to humans.

Kevin Crofton, a behavioral neurotoxicologist at the EPA National Health and Environmental Effects Research Laboratory in Research Triangle Park, North Carolina, points to other problems: "One of the big issues is potential difference in susceptibility of the developing rat brain versus the developing human brain," he says. "For example, epidemiologic studies have shown that a twenty-five percent decrease in maternal T_4 during the first trimester results in decreased IQ in children, [but] there are no rat models that demonstrate this level of sensitivity to

Dennis Kunkel

T_4 decreases. . . . Alternatively, the measures of neurological development in the rat may be crude compared to IQ testing in children."

Many features of brain development are strongly conserved in vertebrates, however. Howdeshell is working to develop a model of the African clawed frog, *Xenopus laevis*, to shed light on gene regulation by thyroid hormone in human processes including brain development. *Xenopus* provides a good model for thyroid hormone effects because the metamorphosis from tadpole to frog is heavily mediated by thyroid hormone. "While *Xenopus* studies cannot be directly extrapolated to human development," says Howdeshell, "the thyroid hormone system is conserved across all vertebrates, including rats and humans, and *Xenopus* undergo thyroid hormone–directed brain maturation similar to the brain development of more complex vertebrates."

The lack of certainty regarding circulating hormone levels as a measure of toxicant effects is also vexing, and researchers are busy devising better assays and end points. Crofton has identified one such end point that he thinks may be a reliable indicator. In research currently under review, he has correlated postnatal T_4 concentrations with hearing loss in rats. These data demonstrate that, at a minimum, a 50% decrease of thyroid hormone in developing rats is needed to adversely impact hearing function.

A further issue is that endocrine disruption research involves to some extent a culture clash between toxicologists and endocrinologists; the methods and typical questions of interest peculiar to each must be harmonized with the other. For example, toxicologists tend to focus on dose–response determinations, whereas endocrinologists historically haven't considered dose response with respect to hormones at all, says Zoeller.

To help harmonize the disciplines and develop a joint research agenda, the NIEHS sponsored two meetings last year: Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk, an international conference that took place 23–25 September 2002 in Research Triangle Park, and Thyroid Toxicants: Assessing Reproductive Health Effects, a workshop held 28–29 April 2003 in Alexandria, Virginia. Many of the most pressing questions were discussed at both, and researchers were encouraged by the interdisciplinary scope of the research program being implemented in response to the EPA's mandate.

The thyroid system is so complex that understanding its normal function is difficult enough, but deciphering environmental disruptions to it is staggeringly convoluted. Yet, the more research reveals, the more pressing the questions become. The thyroid affects nearly every bodily system, and its role in fetal development makes protection of healthy thyroid function imperative. The increasing body of research indicating subtle and possibly additive or synergistic effects of environmental contaminants only adds salience to the issue.

Valerie Brown