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A Primer for the Diagnosis and Treatment of Thyroid Disease

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

By

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A Primer for the Diagnosis and Treatment of Thyroid Disease

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A PRIMER FOR THE DIAGNOSIS AND TREATMENT OF THYROID DISEASE

STATEMENT OF LEARNING OBJECTIVES:

The overall objective of this Primer is to provide nuclear pharmacists with the necessary information to create a clear overview of clinical thyroid issues.

Upon successful completion of this lesson, the reader should be able to:

1. Describe the normal function of the thyroid gland
2. Explain the pathophysiology of certain thyroid diseases
3. Describe the role of nuclear medicine procedures and other medical procedures in the diagnosis, monitoring, and treatment of thyroid disease
4. Consult with nuclear medicine personnel on patient care issues related to the diagnosis and treatment of thyroid diseases

COURSE OUTLINE

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Thyroid Primer

Carol S. Marcus, Ph.D., M.D., ABNM, FACNP

INTRODUCTION

The association of iodine with the thyroid was made in 1896 by Baumann. [1, p4-5] However, the ability to study thyroid function with radionuclides of iodine awaited the invention of the cyclotron in the 1930s, the first of which was at Berkeley, California and the second of which was at MIT in Cambridge, Massachussetts. Various studies were performed with ^{128}I (half-life = 25 minutes), ^{130}I (half- life = 12 hours), ^{126}I (half-life = 13 days), and finally ^{131}I (half-life = 8 days) after its discovery by Glenn Seaborg and Jack Livingood in 1938.[2]

However, therapy was rarely performed because of the small quantities of the radionuclides that could be made on the cyclotron and the long irradiation times necessary, which resulted in high costs of these scarce radionuclides.

The nuclear reactor was invented during World War II to make plutonium for atomic bombs. After the war, the nuclear reactor became a source for large quantities of ^{131}I. The history of the therapy of thyroid cancer and hyperthyroidism with ^{131}I began in 1946 at the end of war and the implementation of the "Atoms for Peace" Program. Numerous medical schools built their own government-funded reactors creating a ready supply of radionuclides, including ^{131}I; these were phased out as various commercial enterprises provided "ready-made" radiopharmaceuticals. Later, in the early 1970s, the concept of the local nuclear pharmacy emerged, leading to chains of commercial nuclear pharmacies, such as we have today.

Accelerator-produced ^{123}I (half-life = 13 hours) became commercially available in the early 1980s. Iodine-123 and had the advantage of having no beta particle and therefore gave low radiation absorbed dose to patients receiving this drug. This radioisotope has a photon, which permits excellent quality images with gamma cameras that had been optimized for ^{99m}Tc, therefore, ^{123}I was ideal for diagnostic purposes. At present, [^{123}I] NaI is widely used for diagnostic thyroid studies, including uptake and imaging, while [^{131}I] NaI is used occasionally

for uptake, exclusively for therapy, and usually for diagnostic imaging in patients with known thyroid cancer in whom remnant thyroid tissue and/or thyroid cancer metastases are sought.

While the normal thyroid tissue shows high avidity for iodide radionuclides and pertechnetate (Table 1), differentiated thyroid cancer tissue usually takes up much less, so much less that thyroid cancer lesions appear as "cold spots" on thyroid scans. However, once the thyroid gland has been removed, the low uptake of differentiated thyroid cancer tissue often appears "hot" relative to the rest of the body on whole body scans.

Table 1

RADIOPHARMACEUTICALS FOR THYROID IMAGING AND UPTAKE					
Radiopharm-aceutical	**Administered Activity**	**Route**	**Time from Dose to Image**	**Time from Dose to Uptake**	**Thyroid Dose[a] rad/μCi Administered**
^{131}I-Na I	50 – 100 μCi	Oral	24 hours	18 – 24 hours	1.30
^{123}I-Na I	200 – 400 μCi	Oral	2 - 6 hours	2 – 6 hours	0.013
^{99m}Tc-Na TcO_4	2 – 10 mCi	IV	20-30 minutes	Not measured	0.0002

a = Based on 25% thyroid uptake Kowalsky, RJ. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine 2nd Edition.* APhA, 2004. Pg 504.

The purpose of this primer is to provide the nuclear pharmacist with the necessary knowledge to function as a consultant to nuclear medicine personnel seeking information regarding the clinical use of radiopharmaceuticals in patients referred for thyroid imaging or therapy. The NRC requirements for physician training for authorized user status to perform thyroid therapy with [^{131}I]NaI are minimal. This sometimes results in situations in which non-nuclear medicine physicians may rely on nuclear medicine technologists for advice, and the technologists or non-nuclear medicine physicians often ask the nuclear pharmacist for information.

ANATOMY OF THE THYROID GLAND

The thyroid gland resides in the anterior neck, near the thyroid cartilage, so named because of its resemblance to a shield. "Thyroid" comes from a Greek word meaning shield. A normal thyroid gland in an adult typically weighs 15-20 grams and consists of two ovoid lobes and connector tissue, the isthmus. See Figure 1. There are a number of anatomical variants that are seen,

including the common pyramidal lobe. This lobe extends from near the isthmus to, or towards the hyoid bone. Sometimes the isthmus is absent. Occasionally, there is agenesis of one thyroid lobe. During embryonic development, the tissue that is to become the thyroid gland migrates caudally from the pharynx to the base of the neck, accompanied by an elongating thyroglossal duct. This duct usually fragments and then degenerates. Ocaisonally, the thyroid fails to descend resultant in lingual thyroid, or does not descend fully from the pharynx to the base of the neck. Sometimes pockets of auxillary thyroid tissue are left behind at various levels of the neck in addition to the thyroid gland being in its usual place. Thyroid tissue can extend caudal to the neck and is substernal. Cysts can also form in thyroglossal duct remnants and may possibly become quite large. Normally, the surgeon will obtain a thyroid scan of the patient before surgery to be sure that he/she does not inadvertently remove the only site of functioning thyroid tissue.

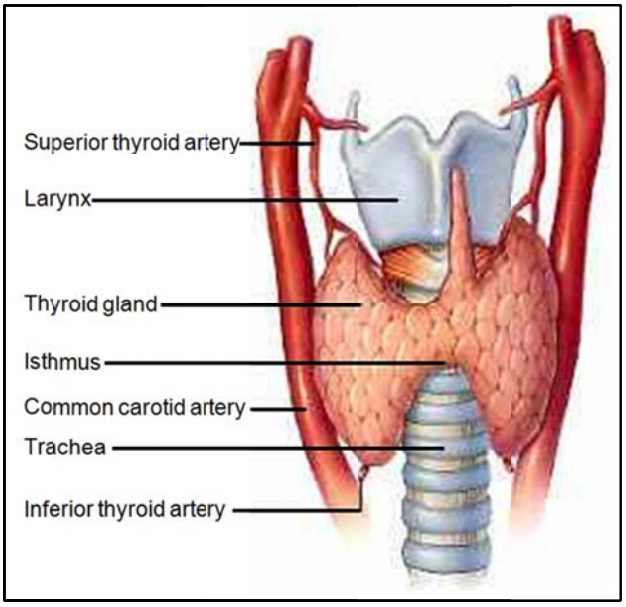

Figure 1. Thyroid Anatomy

Calcitonin-producing C cells of the thyroid are interspersed among thyroid follicles producing thyroid hormones. However, there are other tissues in the body that make calcitonin (brain, gastrointestinal tract, urinary bladder, thymus, and lungs). Consequently, the destruction of the parafollicular C-cells of the thyroid, either from thyroidectomy or radioiodine therapy, has minimal deleterious effects.

Four parathyroid glands, the right and left superior and inferior, are located on the dorsal surface of the thyroid gland. It is essential that during thyroidectomy at least one of the four glands is preserved. Fortunately, radioiodine therapy spares the parathyroid glands. The average energy of the ^{131}I beta particle is 190 kev and its range is only about 0.4 mm in water (similar to tissue). [3,4] The radiation absorbed dose to the thyroid from the ^{131}I beta emission accounts for 94.2% of the total dose, with only 5.8 % coming from the gamma ray. [5]

FUNCTION OF THE THYROID GLAND

The principal function of the thyroid gland the secretion of tetraiodothyronine (T4) and triiodothyronine (T3) to regulate metabolic rate. The thyroid secretes thyroid hormone in response to thyroid stimulating hormone (TSH) secreted by the pituitary. The pituitary releases TSH in response to thyroid releasing hormone (TRH) from the hypothalamus. During the 13th week of gestation , the fetal thyroid begins to make thyroid hormones. [1, p. 17, 5, p. 712]

The source of T3 and T4 synthesis in the thyroid is the thyroid follicle. The follicle is lined by cuboidal follicular cells that synthesize thyroid hormones which are secreted into a colloidal lumen and become bound to thyroglobulin. Hormones are released into the circulation in response to TSH stimulation as shown in Figure 2. Most the thyroid hormone released is as T4. This hormone is less active than T3. Peripheral tissues, especially the liver, contain deiodinases, which convert T4 to T3 as needed.

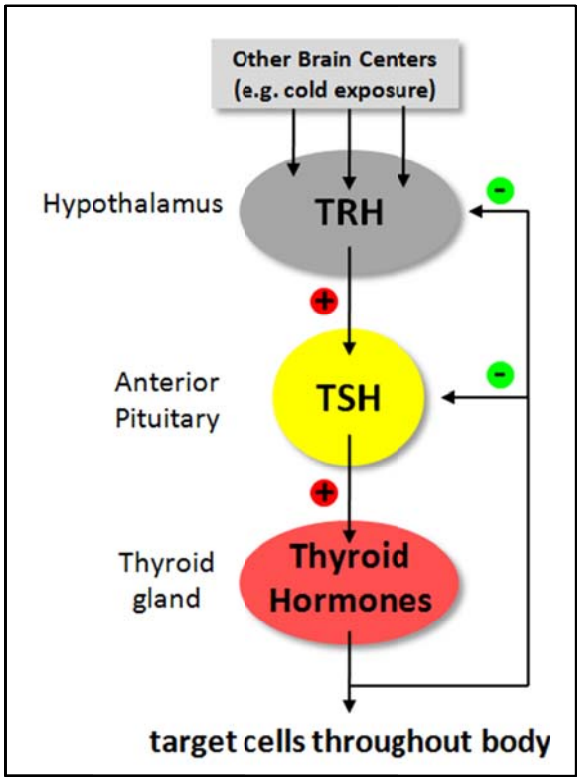

Figure 2. Thyroid Hormone Stimulus & Feedback

Parafollicular C-cells of the thyroid produce calcitonin which acts to reduce blood calcium (Ca^{2+}), opposing the effects of parathyroid hormone (PTH). Calcitonin is the strongest endogenous inhibitor of osteoclastic bone resorption, but its importance in humans is uncertain. [1, p. 837]

DRUGS USED TO TREAT THYROID DISEASE

Hyperthyroid

There are several drugs used to manage hyperthyroidism. See Table 2 for the more common drugs and doses. Beta-blockers block the peripheral action of thyroid hormone. The thioamides (propylthiouracil or PTU and methimazole) block the organification of hormone synthesis. These have little impact on the disease state but must be discontinued about 1 week before performing a diagnostic uptake and scan.

Ipodate sodium (Oragrafin™) is an iodine-containing radiopaque contrast media that may be used for emergency control of severe hyperthyroidism. This drug may be used to block the conversion of thyroid-produced T4 to the much more active T3. The typical dose is 1 gm per day orally or 3 gm every 3rd day. This drug causes iodide flooding and retention which precludes the use of ^{131}I for weeks to months.

Table 2

HYPERTHYROID TREATMENTS	
Drug	**Dosage**
Beta Blockers	
Propranolol	40 – 80 mg four times daily
Atenolol	50 – 100 mg once daily
Metoprolol	25 – 200 mg once daily
Anti-thyroid Drugs	
Propylthiouracil (PTU)	100 mg three times daily, up to 1,200 mg per day
Methimazole (Tapazole™)	10 mg three times daily, up to 60 mg daily

The use of Potassium Iodide (SSKI, iOSAT ™) is not a reliable way to control hyperthyroidism, and is seldom used for this purpose today. Potassium iodide or KI is used to block thyroidal uptake of iodine in workers or patients following accidental ingestion or inhalation of ^{131}I, and to protect the thyroid when ^{131}I is used as a radiolabel for another radiopharmaceutical, such as [^{131}I] metaiodobenzylguanidine (MIBG). It is available as a 1000 mg/mL liquid to take orally with an eye dropper (SSKI) or as a 130mg tablet (iOSAT™). **Note:** Pharmacies using ^{131}I are encouraged to keep an emergency supply of SSKI on hand. When you need it, you need it fast, ideally within an hour.

Hypothyroid

Desiccated thyroid, a drug developed in the late 1800s, has variable T4 and T3 content. Today it is used principally in patients with allergies to one of the excipients commonly found in commercial formulations of synthetic T4. Levothyroxine or a generic T4 is used for full replacement therapy. Liothyronine is synthetic T3 which has a much shorter half-life than T4. Liothyronine is used when a temporary euthyroid state is desired or when the patient is allergic to T4 preparations. Patients must discontinue use of either T3 or T4 prior to a thyroid uptake and scan.

Table 3

HYPOTHYROID TREATMENTS	
Drug	**Dosage**
Desiccated thyroid	32.5 – 130 mg daily
Tetraiodothyronine [T4] (levothyroxine) Synthroid®	0.1 – 0.2 mg daily
Triiodothyronine [T3] (liothyronine) Cytomel ®	50 – 100 μgm daily

Euthyroid

There are two instances where additional drugs may be used to manage thyroid disease or damage. The first is in the preparation of euthyroidic patients for a whole body scan for metastatic survey. These patients need an elevated TSH level for radioiodine localization. For this, recombinant human thyroid stimulating hormone (rhTSH, Thyrogen ™) can be used. Patients are dosed with 0.9 mg IM daily for two days followed by a whole body [^{131}I]NaI dose on day 3.

A commercial preparation of Potassium Iodide (KI) tablets (iOSAT™) is available for thyroid blocking of accidental radioiodine exposure. Tablets of 130 mg daily for adults, 65 mg daily for children, may protect the thyroid from radiation damage if taken 1-4 hours post exposure.

DISEASES OF THE THYROID GLAND AND THEIR THERAPY

Hyperthyroidism

Graves' disease is the most common cause of hyperthyroidism in areas of normal iodine uptake. Graves' is a relatively common disorder that can occur at any age, but most commonly appears in patients aged 20-40 y. In the United States, the incidence of Graves' disease is reported to be 0.02% to 0.4% of the population. In Northern England it is higher, with an incidence of about 1%. In regions with normal iodine intake, the female: male ratio for Graves' disease is approximately 7:1; the ratio is somewhat lower in low iodine areas. The disease may be familial, but the mode of inheritance is unknown. Graves' disease is an autoimmune disease characterized by the overproduction of an antibody to the TSH receptor. This antibody is called "thyroid stimulating immunoglobulin" or TSI. Graves' disease is also associated with other autoimmune diseases such as Hashimoto's thyroiditis, primary hypothyroidism, diabetes, and pernicious anemia.

An “autonomous nodule” means that the thyroid tissue produces thyroid hormone in excess of that needed for homeostasis and is not subject to biochemical feedback. The development of one or more toxic autonomous nodules (Plummer's disease, toxic multinodular goiter) is a fairly common occurrence in patients with longstanding enlarged thyroid gland or goiter. In this instance, the patient has generally been euthyroid for many years, and the etiology of the autonomy is unknown. In both endemic and sporadic non-toxic multinodular goiter, administration of iodides may provoke thyrotoxicosis (Jod-Basedow effect). This is not uncommon in Los Angeles among new immigrants from low iodine areas of the world. It is generally a transient condition that persists until the thyroid "resets" itself. A conservative treatment of watchful waiting is often employed until this happens, usually within 6-8 weeks.

True adenomas are encapsulated and usually compress contiguous tissue. They may be single or multiple. When they are functional, they may become large enough and active enough to cause thyrotoxicosis. Hyperfunctioning thyroid adenomas are very rarely reported to be malignant. As the great majority of "hot" nodules are ablated with [^{131}I]NaI and not biopsied, it is difficult to know whether to what extent malignancy maybe a factor in patients with this presentation.

Hashimoto's disease is a chronic autoimmune thyroiditis, occurring most frequently in middle-aged women. The patient may initially have bouts of hyperthyroidism, but in time will become hypothyroid as the gland is progressively destroyed. It is a relatively common disease, probably responsible for a significant portion of cases of idiopathic hypothyroidism. It is not amenable to treatment with PTU, methimazole, or [^{131}I[NaI, as the extra T4 comes from destroyed thyroid cells that leak. Iodine uptake is usually very low during inflammatory episodes, 0-5 %, because the gland is not functioning normally during active attacks. Beta-blockers are the treatment of choice until the patient becomes hypothyroid, in which case T4 replacement is necessary.

Subacute or De Quervain's thyroiditis is sometimes viral in origin, is frequently painful but may be painless, and is self-limiting often abating within about six weeks. Often the patient requires no treatment other than aspirin for pain from swelling. Occasionally, a beta blocker is used to treat the transient, usually mild, hyperthyroid symptoms. The disease is characterized by a very high erythrocyte sedimentation rate (ESR) and a very low radioactive iodine uptake (RAIU).

Treatment of Hyperthyroidism

a) Medical

The medical treatment of hyperthyroidism has three general goals: (1) quick cessation of adverse cardiac effects, (2) inhibition of over activity of the gland, and (3) to buy time. The cessation of adverse cardiac effects is achieved by beta blockers, often in large doses. Asthma and congestive heart failure contraindicate beta blockers such as propranolol. However, if the cardiac failure is felt to be primarily high output failure induced by thyrotoxicosis, propranolol may still be used. Alternatively, atenolol or metoprolol may be used. Several drugs are used to inhibit overproduction of thyroid hormone. Propylthiouracil inhibits iodide uptake, organification, and peripheral conversion of T4 to T3. Methimazole acts similarly to PTU but, does not inhibit the peripheral conversion of T4 to T3. Both drugs can inhibit antibody production. Iodinated contrast agents such as Oragrafin^{TM} are particularly effective in inhibiting T4 to T3 conversion by the liver, the most important organ for peripheral (non-thyroidal) conversion. Buying time makes good sense. A significant number of patients with new onset Graves' disease will demonstrate spontaneous remission after 6 months to 1 year of medical treatment, and will require no further therapy. The Jod-Basedow phenomenon will usually remit as the patient "resets" his thyroid gland. Buying time is also necessary while preparing the patient for other therapy, i.e. radionuclide administration or, rarely, surgery.

b) Radioiodine

Today, [^{131}I]NaI is used exclusively as the iodine radionuclide of choice in all thyroid therapy. It was often used for thyroid uptake and scan in the past. The widespread availability of [^{123}I]NaI (gamma emitter, half-life of 13 hours) has now replaced the diagnostic use of [^{131}I]NaI because of superior images and far lower radiation absorbed dose. [^{131}I]NaI is also used almost exclusively for metastatic surveys, whole body scans used for the diagnosis of thyroid cancer metastases or persistent normal thyroid remnants post-surgery. [^{131}I]NaI is administered orally as either a solution or capsule. Because concentrated [^{131}I]NaI is quite volatile, all commercially available [^{131}I]NaI solutions are stabilized to prevent volatility, generally by making the solution highly basic. In very rare situations, [^{131}I]NaI is given intravenously. However it is not a commercially-available product and therefore it must be compounded as a sterile and pyrogen-free product with its pH and osmolarity adjusted to physiologic range. **Note: Administration of**

[^{131}I]NaI through a feeding tube is not advised due to potential adsorbtion onto the walls of the tube.

The natural course of untreated Graves' disease is hypothyroidism, as the persistent autoimmune attack on the gland eventually destroys the thyroid. Treatment with [^{131}I]NaI causes thyroid destruction and rapid onset of hypothyroidism, usually within 6 weeks. If a patient has not become hypothyroid within 3-4 months, another [^{131}I]NaI administration should be given. It is reasonable to give the same dose that was given the first time. It is rare to require a third dose of [^{131}I]NaI if the first dose was estimated to give about 120 Gy (12,000 rads).

For many years, physicians tried to give a dose of [^{131}I]NaI for Graves' disease that was "just enough" to result in a euthyroid state. This proved nearly impossible. Partial destruction of the gland usually results in regrowth and recurrence of hyperthyroid symptoms. The contemporary practice is to aim for thyroid destruction and then manage the patient on thyroid hormone replacement.

The following equation is useful for estimating the administered activity of [^{131}I]NaI for the treatment of Graves' disease. **Note:** This estimate is often inaccurate, partly due to the inaccuracy in estimating the needed parameters, and partly due to individual variation:

$$\mu\text{Ci}[^{131}\text{I}]\,\text{NaI} = \frac{(\text{Rads})(\text{Physical Half}-\text{life})(\text{Thyroid wt in grams})}{(\text{Gm}-\text{rad}/\mu\text{Ci}\ ^{131}\text{I})(\text{Effective Half}-\text{life})\ (\text{Max Uptake})}$$

Radiation absorbed dose is typically 12,000 Rads (120 Gy)

Physical half-life is 8 days

Thyroid weight in grams ranges from 15-20 (normal) to 500 grams (gigantic)

Gm-rad/μCi for ^{131}I is 120

Effective half-life averages 4.3 days for hyperthyroid patients, but can vary from < 1 to 8 days.

$$T_{1/2\,\text{Effective}} = \frac{T_{1/2\,\text{Biological}}\ \text{x}\ T_{1/2\,\text{Physical}}}{T_{1/2\,\text{Biological}} + T_{1/2\,\text{Physical}}}$$

The maximum thyroid radioiodine fractional uptake is about 0.1-0.25 in normals and about 0.35-0.9 in
Graves' disease. The maximum uptake in normals occurs approximately 48 hours post-administration, but in hyperthyroid patients it may occur within 24 hours.

Typical administered activities of [^{131}I]NaI range from 185 to 1110 MBq (5 to 30 mCi), but administering less than 370 MBq (10 mCi) in an adult nearly always results in having to repeat the procedure. Lower doses may be used in children. On occasion, larger doses of 1850-5550 MBq (50 - 150 mCi,) may be used for very large glands or when low uptakes and short effective half-lives are observed. In one such case, 10.2 GBq (275 mCi) was required for a patient on amiodarone who had a very low fractional peak uptake and a very short efffective half-life. (Amiodarone contains iodine, and floods the iodine pool causing prolonged iodine retention.) Similar situations can apply to patients on PTU who cannot be taken off the drug because of life-threatening arrhythmias.

If one wants to make reasonable estimates of radioactive iodine uptake (RAIU) and effective half-life, one can administer 14.8 MBq (400 μCi) of [^{123}I]NaI (some physicians use 0.27 MBq (10 μCi) [^{131}I]NaI) and measure uptakes 1-2, 4-6 hours, and then at 24, 48, and 72 hours later. Plotting the resultant uptake data on semi-logarithmic paper will give one the effective half-life. Most physicians obtain only a 24 hr RAIU, estimate gland size, and assume an average effective half-life of 4.3 days (or some other value). Other physicians may not obtain uptake data and chose to just give an arbitrary "one size fits all" dose, ranging from 259 to 1110 MBq (7 to 30 mCi). A dose of 1110 MBq (30 mCi) is usually more than what is needed to ablate most thyroids the first time.

If patients have Plummer's disease, the calculation shown above is not used. It is common practice to use 370 MBq (10 mCi) for a small hot nodule, 740 MBq (20 mCi) for a medium hot nodule, and 1110 MBq (30 mCi) for a large hot nodule or multiple hot nodules. This scheme works well and seldom requires retreatment. Hyperthyroid patients with Plummer's disease have suppressed normal thyroid tissue. Thus, only the hot nodule taking up the ^{131}I and making thyroid hormone. Therefore, only the hot nodule is burned out with ^{131}I therapy. The normal

tissue is spared, and the patient usually becomes euthyroid after therapy. Th do not typically requiring hormone replacement unless multiple hot nodules were present resulting in the destruction of a large portion of otherwise normal gland.

In older patients or whenever serious cardiopulmonary disease is present, it is often a good idea to deplete the thyroid gland of stored thyroid hormone (e.g. with PTU for about 3 months). This avoids any worsening of thyrotoxicosis or the occurrence of "thyroid storm" during the first two weeks following [^{131}I]NaI treatment when thyroid cells are destroyed and thyroid hormone leaks out into the circulation. While patients are typically taken off PTU or methimazole for about a week before therapy with [^{131}I]NaI, beta blockers may be used to control symptoms for as long as necessary.

In the early days of [^{131}I]NaI therapy, there was concern about the possibility that [^{131}I]NaI therapy might increase the incidence of leukemia or myelodysplastic syndrome. Studies of about 35,000 hyperthyroid patients for up to 50 years have shown that while there is some increased leukemia related to the length of time that hyperthyroidism was untreated, therapy with [^{131}I]NaI did not result in any significant increase in leukemia relative to patients treated surgically.[6] Consequently, there should be no reservation in treating children or young adults with [^{131}I]NaI.

On the other hand, great care should be taken to avoid any [^{131}I]NaI administration to pregnant or lactating patients. The fetal thyroid begins accumulating iodine after 3 months, and even very small quantities of ^{131}I can severely damage or destroy fetal or newborn thyroids. Always observe the precaution of obtaining a pregnancy test prior to any [^{131}I]NaI administration. Clinicians should NOT rely on menstruation history. Hyperthyroid patients have scant bleeding during menses, which is easily confused with spotting observed during the first trimester of pregnancy. The patient may think she has had her period, when in fact she hasn't. When counseling a female patient before [^{131}I]NaI therapy for hyperthyroidism, one should strongly recommend avoiding pregnancy for at least 4 months. This is the time that a second dose of [^{131}I]NaI may be given, should it become necessary. Nuclear medicine personnel should advise the patient to wait until her thyroid function is normal before risking a pregnancy, because she cannot be treated while pregnant. If a patient becomes pregnant shortly after receiving [^{131}I]NaI,

this is not a disaster. The embryo or fetus will not be taking up iodine until virtually all of it has left the mother's body, and the radiation dose is otherwise small and not of real concern. Further, there has been no evidence that patients treated with [^{131}I]NaI for hyperthyroidism have decreased fertility or increased mutations in offspring. [7]

c) Surgery

The preferred treatment of hyperthyroidism is medical in combination with radioiodine, as indicated, and not surgical in the vast majority of cases. Surgery is a consideration as definitive therapy under the following circumstances: pregnancy, large toxic goiter compressing neighboring structures, non-compliance, inability to obtain replacement levothyroxine (it is not available in some countries), and pathologic fear of radiation.

Pre-operative patients are treated with PTU or methimazole to deplete the gland of thyroid hormone and are given SSKI for 7-10 days to decrease thyroid gland vascularity. The surgical procedure of choice is a subtotal thyroidectomy leaving approximately 5 grams of thyroid tissue on each side. This residual thyroid tissue is designed to result in an incidence of hypoparathyroidism of less than 15% and to preclude injury to the recurrent laryngeal nerve or devascularization of the parathyroid glands. The incidence of recurrent hyperthyroidism is less than 10%. The incidence of eventual hypothyroidism is approximately 10% at 1 year and 25% at 15 years post-op. [7]

Thyroid Cancer

The frequency of thyroid carcinoma is surprisingly high as defined by pathologic demonstration. However, the occurrence of clinically evident thyroid cancer is much lower and the death rate from thyroid carcinoma is very low. For example, the prevalence of nodular goiter is about 4%, and up to 20% of these show areas of carcinoma by examination of surgical specimens. [8] On the other hand, the American Cancer Society estimated that in 2010 there would be only 44,670 new cases diagnosed in the United States, and that about 1,690 deaths from this cancer would occur during that year. [9] The death rate for papillary cancer, which represents about two thirds of all thyroid cancer, is quite low and age dependent (worse with increasing age). [10] A series from the Lahey Clinic reported that the gross 20-year death rate from papillary thyroid cancer or its

surgical treatment was 10.9%. [10] This series consisted of 441 patients seen from 1931 to 1960 with a minimum 15-year follow up. Death rate for patients aged 50 years or less at diagnosis was 3.8%, whereas that for patients older than 50 years was 29%. The 15-year death rate for patients of all ages with operable papillary cancer treated during the years 1950-1960 was 8%.

Follicular thyroid cancer accounts for about 18% of thyroid cancer in a Mayo Clinic series. The 20-year Lahey Clinic gross death rate for all patients with follicular cancer diagnosed prior to the age of 41 years was 6.8%. Combined death rates for operable differentiated cancer found in men below the age of 41 years and women below the age of 51 years was only 1% during the years 1951-1960. [11] Medullary thyroid carcinoma represents about 6-7% of thyroid carcinoma. Older patients have a greater likelihood of tumor metastases. Among all patients with medullary thyroid carcinoma having surgery at the Mayo Clinic through 1975, the mortality rate was 20% at 5 years and 33% at 10 years. [12] Anaplastic carcinoma accounts for the remaining approximately 14% of thyroid cancer. It usually affects the elderly and is highly malignant and usually rapidly fatal due to extensive local invasion, which is refractory to radiation and chemotherapy.

Papillary, follicular, and mixed papillary/follicular cancers are treated with [^{131}I]NaI, because most of these cancers concentrate iodine to some extent. Medullary thyroid cancer, anaplastic thyroid cancer, and papillary, follicular, and mixed papillary/follicular thyroid cancers that have lost the ability to concentrate iodine cannot be successfully treated with any radiopharmaceutical at present.

The workup of thyroid cancer usually begins with the discovery of a hard thyroid nodule or mass. A radioiodine scan demonstrating a cold (non-functioning) region is often followed by ultrasound to rule out a cyst. Cysts are rarely malignant. Cold, solid nodules have a 10-30% chance of being malignant, depending upon the series cited. [13] Sometimes aspiration biopsy is performed, but due to occasional false-negative results, excisional biopsy is sometimes performed. If the tissue is malignant, it is generally agreed that a near-total thyroidectomy is the best plan. In the case of papillary, follicular, or mixed papillary-follicular carcinoma, follow-up thyroid ablation with [^{131}I]NaI is characteristically recommended once the TSH is 50 IU or

greater (or rhTSH is used). The usual dose for a small, encapsulated tumor without extracapsular invasion or distant metastasis is about 3700 MBq (100 mCi). A higher dose of [^{131}I]NaI is administered if functional (iodine-avid) thyroid cancer metastases are discovered or if the original tumor is large or if it extends beyond the thyroid capsule. Typical doses are about 5550 MBq (150 mCi) for moderate size primary tumors without local spread or metastasis, 7400 MBq (200 mCi) with mild to moderate local spread and/or metastases, and 11.1 GBq (300 mCi) with extensive spread and metastases.[14] Sodium iodide [^{131}I] is not usually useful for treating brain metastasis due to the poor distribution to the brain. Typically, brain metastases are evidence of advanced and widespread disease. This usually means a dedifferentiation of at least some of the tumor into non iodine-avid cells. These “iodine-negative” cells are not killed by the radiation from [^{131}I]NaI unless from bystander radiation from adjacent iodine-avid cells.

It is important to realize that patients do not die from an iodine-avid tumor, which can always be killed, but rather, from non iodine-avid or iodine-negative tumor, which can only be killed by surgical excision or sometimes by external beam radiation. For this reason, it is important to use generous doses of [^{131}I]NaI to "overkill" iodine-avid cells, in order to kill adjacent iodine-negative cells if they exist. While some physicians use calculated doses to just kill iodine-positive cells, other physicians do not agree with this practice. Once iodine-negative cells spread widely, the patient will die. There is no chemotherapy or other established radiopharmaceutical therapy which is helpful, so some physicians attempt to kill the iodine-negative cells when one can, using the iodine-positive cells as the radiation source. This concept of “bystander” radiation killing iodine-negative cancer cells is theoretical only. There is no data supporting this practice.

Follow-up of treated patients is usually done with metastatic surveys performed with 18.5-370 MBq (0.5-10 mCi) [^{131}I]NaI. [15] This is done by taking the patient off replacement levothyroxine for a month (sometimes 5-6 weeks is necessary) until the TSH is approximately 50 IU or higher. Liothyronine can be given for the first two weeks to keep the patient comfortable, and then nothing for two weeks while the TSH rises. The theoretical concept of "thyroid stunning" has gained quite a bit of acceptance in recent years and led to the increased use of low [^{131}I]NaI doses, such as 500 μCi for a metastatic survey. The limited data available does not support a decreased uptake of a therapy dose after a diagnostic dose of [^{131}I]NaI (the concept of

"stunning").[16] However, the treatment doses recommended above are sufficiently high so that if "stunning" does occur, there is still plenty of radiation from [^{131}I]NaI absorbed to achieve desired therapy.

As an alternative, recombinant human TSH (Thyrogen®) has become available. This may be used instead of stopping levothyroxine and causing a natural rise of TSH. It is much more pleasant for the patient, but expensive. Recombinant human TSH may also not be as effective in causing ^{131}I uptake into the tumor or thyroid remnant because euthyroid patients excrete ^{131}I more rapidly through the kidneys than do hypothyroid patients, leaving less available to get taken up by the thyroid cancer. If the patient is using it, this is another reason to administer generous ^{131}I doses. Thyrogen® is FDA-approved for diagnostic imaging as well as therapy. The half-life for renal clearance of [^{131}I]NaI is about 12 hours in hypothyroid patients and about 8 hours in euthyroid patients, assuming normal renal function.

Serum thyroglobulin (Tg) levels have been followed as a marker for tumor recurrence since the early to mid-1980s. (17) It is a very good substitute for periodic metastatic surveys, but it is not perfect. Thyroglobulin is the protein that binds thyroid hormone in the thyroid follicle. A very small percent of thyroid cancers become Tg-negative while still retaining the ability to take up ^{131}I. Physicians generally rely on Tg levels, and perform metastatic surveys when the Tg rises. If the patient is known to have anti-Tg antibodies, which is common, or if the patient is at significant risk of recurrence, physicians use both the Tg and the metastatic surveys. Once a patient appears to be tumor-free and has no more functioning thyroid tissue, following serum Tg levels every 6 months to a year is usually sufficient for follow-up purposes. The same interval would be used for the metastatic surveys. After 5 negative years, every two years is usually sufficient. [17]

The American Thyroid Association (ATA) has published extensive guidelines for the management of differentiated thyroid cancer in 2006 and again in 2009. These guidelines are extensive and well documented. Due to the fact that many small differentiated thyroid cancers (less than 1 cm in diameter) that have not spread at all are cured by surgery or would not have

behaved malignantly anyway, the ATA does not recommend postoperative radioiodine ablation for them.[18]

The doses of [^{131}I]NaI used for the treatment of thyroid carcinoma are commonly 10 to up to 100 times the doses used to treat hyperthyroidism because thyroid cancer tissue is usually much less iodine-avid than hyperthyroid or normal thyroid tissue. At these high levels, radiation dose to bone marrow and reproductive organs is a consideration. A dose of 37 MBq (1 mCi) of ^{131}I results in about 6.7 mGy (0.67 rads) to bone marrow. A few cases of leukemia have been reported in patients who have received a total dose of over 37 GBq (1 Ci), but this exceedingly rare complication is not of major concern so long as a thyroid cancer remnant is still concentrating iodine. [19] Females of reproductive age should best avoid pregnancy until they are cancer-free, as ^{131}I would not be able to be used for diagnosis or therapy during pregnancy or lactation. Patients should wait an absolute minimum of a month in order to repair theoretical radiation damage to ova and documented damage to sperm.[20]

While outdated radiation protection regulations required hospitalization of patients given 1110 MBq (30 mCi) ^{131}I or more, the NRC now requires hospitalization only if there is a reasonable possibility of a member of the public getting a radiation dose of 5 mSv (500 mrem) or more from the patient. The primary reasons to hospitalize patients receiving [^{131}I] NaI are medical instability, urinary incontinence, a tracheostomy requiring suctioning (this fluid is very high in ^{131}I), inability to follow simple safety precautions, and living arrangements that are not conducive to precautions, such as the whole family sleeping in the same bed, one bathroom for multiple families, being homeless, or in a group-living situation such as a drug rehabilitation facility.

Euthyroid Goiter and Hyperfunctioning Nodules in Euthyroid Patients

The treatment of goiter is levothyroxine, in order to decrease endogenous TSH and stop thyroid stimulation. Goiters may shrink or at least stop growing. Hyperfunctioning nodules will hopefully be suppressed; otherwise they may become autonomous and the patient will become hyperthyroid. It does not make sense to try to suppress a patient with a hot nodule who is already

hyperthyroid. By definition, the nodule is not suppressible. [^{131}I]NaI therapy is not indicated for the treatment of either of these euthyroid states.

PATIENT MANAGEMENT AFTER TREATMENT OF THYROID DISEASE

Graves' Disease

Radioiodine ablation of the thyroid should occur within approximately 6 weeks following therapy, at which time the patient needs to begin levothyroxine therapy. The patient should be monitored until the replacement dose is optimized and serum free T4 is in the normal range. This is usually done by the patient's internist or endocrinologist, but may also be done by the nuclear medicine physician. Once an appropriate dose of levothyroxine is determined, the patient remains on that dose indefinitely. Older patients may require a diminution of the dose, and pregnant patients may require an increase in the dose, especially in the second and third trimesters.

Autonomous ("Hot") Nodules

The patient should become euthyroid after radioiodine treatment and require no medication. However, patients who have developed one autonomous nodule are at high risk of developing recurrence. These patients should be followed annually by their physician to ensure that any recurrence of new autonomous nodules are promptly treated.

Differentiated Thyroid Cancer

Endocrinologists generally follow these patients. After initial surgery and radioiodine ablation of remnant thyroid tissue, the patient becomes hypothyroid and needs levothyroxine. However, the dose should be somewhat high, so as to keep the TSH below normal. [18] That is, the patients are made borderline hyperthyroid on purpose. The serum thyroglobulin is often followed annually, and any elevation is followed by a metastatic survey. Some high-risk patients, or those who have thyroglobulin antibodies, will be given metastatic surveys. They will need to discontinue levothyroxine to raise their TSH before receiving [^{131}I]NaI unless they receive liothyronine.

In the event that a metastatic survey shows a hot focus, a therapy dose of [^{131}I]NaI should follow, using the same administered activity criteria as discussed in the section above titled: "*Thyroid Cancer*".

In the event that a patient's serum thyroglobulin level is rising, but the metastatic survey is negative, some clinicians will request radioiodine therapy anyway, positing that the low dose of radioiodine used in the metastatic survey was insufficient to identify the focus, but that the therapy dose may identify additional foci. This is sometimes the case, especially with the low doses some nuclear medicine physicians use for metastatic surveys. If one administers, 3700 MBq (100 mCi) of [^{131}I]NaI, followed by imaging in a week and still does not show any tumor focus, then radioiodine treatment should be abandoned and an [^{18}F]FDG PET scan should be performed.[18] As the cancer becomes more and more undifferentiated, and less and less likely to concentrate iodine, it is more and more likely to be seen on the PET scan. If the focus is in a chain of lymph nodes in the neck, a surgeon may elect to surgically remove all the lymph nodes on that side. The thyroglobulin will then often decrease. If the focus is not surgically resectable, however, there are no other good treatments available at present.

HEALTH PHYSICS CONSIDERATIONS WITH THE USE OF [^{131}I]NaI

According to Title 10 CFR Part 35.75 within the NRC's medical regulations, patients may be treated as outpatients so long as the licensee believes that the total radiation absorbed dose to any other person is not likely to exceed 5 mSv (500 mrem). Instructions to patients, parents, or guardians, including written instructions, are necessary if any other person is likely to receive over 1 mSv (100 mrem). (For more information about patient release criteria, the reader is referred to NRC NUREG 1556, Appendix U *Release of Patients or Human Research Subjects Administered Radioactive Material.)[http://www.nrc.gov/reading-rm/doc-collections/nuregs/staff/sr1556/v9/r2/]*

Consequently, it is necessary to know how to calculate the radiation absorbed dose to others originating from the patient, and to provide written as well as verbal instructions.

Radiation Absorbed Dose Calculations

The methodology for calculation of absorbed dose from an external source, such as a patient or a spill on the floor, is described in NCRP No. 37, 1970, Appendix I.[21] This method is simple and uses straightforward assumptions, but as more information is available, the method can also accommodate increased complexity.

For example, when the external source is a spill on the floor, the physical half-life will apply. When the external source is a patient with a radiopharmaceutical, one can combine the biological half-life with the physical half-life to determine the effective half-life. The effective half-life may then be used in the equation instead of the physical half-life.

Another example would be the specific gamma ray constant, which assumes an unshielded point source. Patients are not unshielded sources, and if shielding can be measured or calculated, a different specific gamma ray constant should be used that corrects for patient shielding. Geometric sources other than a point may be used also, but this is somewhat more complex and will not be covered here.

Another example involves more than one biological process as the radiation source. For instance, [^{131}I]NaI given to a patient with hyperthyroidism could involve 60% going to the thyroid with an effective half-life of 4 days, and 40% being non-thyroidal, with an effective half-life of 8 hours. In this case, one would calculate the absorbed dose from the thyroid component separate from the dose from the non-thyroidal component, and add them together.

Another example involves the time spent close to a radiation source. It is actually hard to spend more than 6 hrs a day close to another person (e.g. 1 meter away) unless the two sleep together. Therefore, if they are not sleeping together, a conservative default value is 6 hr. or 0.25d. However, if the only exposure to a patient is driving him home after radiopharmaceutical administration, and the drive takes 2 hrs., and the patient sits in the back seat on the right, then the time is only 2/24 or 0.083d and the distance is more like 2 meters (or 200 cm) than 100 cm. The object of these calculations is often to assure that no member of the public gets more than 5 mSv (500 mrem) from a patient who has been given a radiopharmaceutical. By modeling one's

system realistically, one will find that most therapy patients may be treated as outpatients. Patients who are bedridden, incontinent, who require special care, or who have significant contamination sources, need special consideration before making them outpatients. However, one can make simple but useful models for a caregiver to estimate absorbed dose using this methodology, and even complex patients may be treated as outpatients with the right caregiver.

The general equation follows, along with the specific gamma ray constants for ^{131}I.
Next come two problems that will provide practice using the equation.

The Equation[22]*:*

$$D_{(t)} = \frac{(24)\ (1.44)\ (\Gamma)\ (mCi)\ (T)\ (1 - e^{-0.693t/T})}{cm^2}$$

Where:

$D_{(t)}$ = accumulated exposure at time t, in roentgens (assume the usual approximate equality to rads and rems of unity)

mCi = starting activity in millicuries

T = physical half-life in days. If effective half-life is to be used, $T_{eff} = T_B \times T_p / T_B + T_P$

r = distance from the center of gravity of the source to the center of gravity of the person in question, in centimeters.

t = exposure time, in days

Γ = the specific gamma ray constant for an unshielded source in R/mCi-h at 1 cm.

24 = the number of hours in a day

1.44 = the factor by which the half-life is multiplied to get the mean life or average life. 1.44 = 1/0.693. Recall, the half-life is 0.693/k, the decay constant. The mean life or average life is 1/k. Also, (24)(1.44)= 34.6, which is generally used to replace the two terms.

Note: The specific gamma ray constant is in hours. T and t are in days, which is why you need the factor of 24. If you use hours for T and t, you may drop the 24.

The specific gamma ray constant for an unshielded point source of ^{131}I is 2.2 R/mCi-h at 1 cm.

^{131}I, when dispersed in a patient, has a measured gamma ray constant of about 1.7 R/mCi-h at 1 cm. This was measured in a group of patients immediately after swallowing [^{131}I]NaI. (22)

Problem 1:

A patient requires 1850 MBq (50 mCi) [^{131}I]NaI for therapy of Graves' disease. Her uptake is 55%, her biological half-life is 5 days, and her renal function is normal. If treated as an outpatient, what is the highest expected radiation dose to someone with whom she shares a household?

Assume she sleeps alone and does not share eating utensils. Assume a 25% tandem person at 1 meter (very conservative).

$$T_E = \frac{T_B \text{ x } T_P}{T_B + T_P} = \frac{5 \text{ x } 8}{5+8} = \frac{40}{13} = 3.1 \text{ days}$$

$$D_0 = \frac{34.6\,(2.2)\,(50)\,(3.1)\,(1 - e^{-0.693(4)/(3.1)})}{4\,(100\,cm^2)} + \frac{34.6\,(1.7)\,(50)\,(0.45)\,(0.33)\,(1 - e^{-0.693(4)/(3.1)})}{4\,(100\,cm^2)}$$

$$D_0 = 0.162 + 0.011 = 0.17R = 170 \text{ mrem } (1.7mGy)$$

(The biological half-life of the non-thyroidal component in a person with normal kidneys is about 8 hours or 0.33 days.) Note: We use the specific gamma ray constant for the thyroidal component (as it approximates a point source) while we use the measured gamma ray constant for the non-thyroidal component.

Problem 2:

A thyroid cancer patient requires 7400 MBq (200 mCi) [^{131}I]NaI for therapy. Assume that uptake in the postoperative thyroid remnants is 1% and that the patient has normal renal function. If treated as an outpatient, what is the highest expected radiation dose to someone with whom he shares a household?

$$D_{0.25} = \frac{34.6(2.2)(2)(7.3)(1-0)}{200\,cm^2} + \frac{34.6(1.7)(198)(0.33)(1-0)}{200\,cm^2}$$

The biological half-life of iodine in normal thyroid tissue is 80 days.

$$T_E = \frac{T_B \text{ x } T_P}{T_B + T_P} = \frac{80 \text{ x } 8}{80+8} = \frac{640}{88} = 7.3 \text{ days}$$

$D_{0.25} = 0.0278 + 0.0961 = 0.12$ R

= 120 mrem (1.2 mSv)

RADAR

The above calculations of radiation absorbed dose are available in an interactive web site called RADAR, the RAdiation Dose Assessment Resource. This is an extremely useful web site. The url to access RADAR is www.doseinfo-radar.com for the home page, and www.doseinfo-radar.com/ExposureCalculator.html for the Exposure and Dose Calculator.

Advice to Patients

After estimating the radiation absorbed dose it is important to talk to the patient and tailor advice to that patient's educational level, cultural background, socioeconomic circumstances, and life style. If for any reason the patient cannot be appropriately educated, or the patient is reasonably expected to be non-compliant, the physician should seriously consider hospitalizing the patient.

Control of body fluid contamination is an important concern following treatment with [^{131}I]NaI. Urine, sweat, and saliva will contain significant quantities of ^{131}I. Patients should avoid splashing urine. Male patients should be asked to urinate sitting down for the first few days following therapy. Patients should shower daily, and bed and bath linens, including pajamas and nightgowns, should be laundered in a separate load in the washing machine for three days following therapy. To avoid saliva contamination there should be no sharing of eating utensils, glasses, or drink containers (sodas), and no kissing. Patients who are incontinent are usually hospitalized and catheterized.

The care of babies and young children should be delegated to someone else in the household, or the children should stay with a friend or relative for several days to a week following therapy, depending upon the dose calculations. Patients should sleep alone for several days to a week, again depending upon the dose calculations. They should try to keep a minimum distance of two meters from others in the household and no closer than one meter for short periods of time. Ideally, the patient should not be involved in the preparation of meals for others. If cooking is necessary, the patient should wear protective attire such as disposable gloves to avoid getting sweat into the food.

Patients who work may continue to work so long as they do not remain close to anyone for any significant amount of time. It may also be advisable to keep patients out of work for several days. Patients treated with [^{131}I]NaI should be advised not to stay in hotel or other similar accommodations. These facilities are less controlled and highly accessible to the public. If radiation is detected within a hotel or other public, facility great and often unnecessary attention maybe brought to the patient. In general, patients should be advised not to use public transportation such as trains, planes, buses, or other carriers that would place them in close proximity to a single person for an extended period of time.

Conclusion

At the conclusion of World War II, Congress passed the Atomic Energy Act of 1946 making radioisotopes available for civilian use. In December of 1946, Sam Seidlin published an article in JAMA describing the complete disappearance of multiple functioning metastases in a patient after thyroidectomy for thyroid cancer. This article, considered the most important published in nuclear medicine, sparked public interest and forced Congress to support the medical use of radioactive materials. In 1951, [^{131}I]NaI became the first radiopharmaceutical approved for human use by the Food and Drug Administration.[23] More than 60 years later this radiopharmaceutical remains the treatment of choice for treating hyperthyroidism and thyroid cancers.

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ASSESSMENT QUESTIONS

1. Which of the following hormones is ***not*** made by the thyroid gland?

    a. Triiodothyronine
    b. Tetraiodothyronine
    c. Calcitonin
    d. Parathormone

2. Which of the following radionuclides of iodine emits ***no*** beta particle?

    a) ^{123}I
    b) ^{131}I
    c) ^{128}I
    d) ^{130}I

3. All of the following are anatomical variants of the thyroid gland ***except:***

    a) pyramidal lobe
    b) lingual thyroid
    c) abdominal thyroid
    d) substernal thyroid

4. The fetal thyroid concentrates iodine after the:

    a) 12th week of gestation
    b) fourth week of gestation
    c) sixth week of gestation
    d) second trimester of gestation

5. All of the following drugs may be used to ameliorate hyperthyroid symptoms ***except***:

    a) propranolol
    b) levothyroxine
    c) metoprolol
    d) atenolol

6. All of the following drugs are used to treat hyperthyroidism ***except***:

    a) propylthiouracil
    b) Oragrafin®
    c) methimazole
    d) liothyronine

7. The following conditions result in hyperthyroidism ***except***:

a) lingual thyroid
b) Graves' disease
c) Hashimoto's thyroiditis
d) autonomous nodules

8. Graves' disease in regions with normal iodine in the diet is most commonly seen in:

a) middle-aged men
b) elderly females
c) teenagers
d) women aged 20-40

9. Jod-Basedow syndrome is seen in patients:

a) with genetic predisposition
b) from low iodine intake areas who move to normal iodine intake areas
c) who have had surgically treated hyperthyroidism and have relapsed
d) who have had Hashimoto's thyroiditis for an extended period of time

10. Patients with sustained hyperthyroidism may be treated with all of the following ***except***:

a) PTU or methimazole
b) [^{131}I]NaI
c) recombinant TSH
d) surgery

11. Contraindications to treatment of hyperthyroidism with [^{131}I]NaI are all of the following ***except***:

a) pregnancy
b) lactation
c) pathologic fear of radiation
d) diabetes

12. Differentiated thyroid cancer includes all of the following ***except***:

a) anaplastic thyroid cancer
b) papillary thyroid cancer
c) follicular thyroid cancer
d) mixed papillary-follicular thyroid cancer

13. The death rate from papillary thyroid cancer is approximately:

a) 1 %
b) 10%
c) 50%
d) 90%

14. The initial treatment of differentiated thyroid cancer is generally:

a) near-total thyroidectomy + remnant ablation with [^{131}I]NaI
b) thyroid lobectomy + remnant ablation with [^{131}I]NaI
c) metastatic survey + focal ablation with [^{131}I]NaI if positive
d) [^{131}I]NaI thyroid ablation + metastatic survey in one year

15. The theoretical concept of "thyroid stunning" is:

a) halting the spread of metastases with [^{131}I]NaI treatment
b) ablate the primary tumor with [^{131}I]NaI treatment
c) inhibiting tumor uptake of a therapy dose of [^{131}I]NaI after a diagnostic dose of [^{131}I]NaI
d) preventing primary cancer uptake of a metastatic survey dose of [^{131}I]NaI after a therapy dose of [^{131}I]NaI

16. Thyroglobulin is:

a) a protein that binds thyroid hormone in the circulation
b) a protein that binds thyroid hormone in thyroid follicles
c) an immunoglobulin made against thyroid cancer
d) an immunoglobulin made against normal thyroid tissue

17. Thyrogen® is used to:

a) replace thyroid function after thyroidectomy
b) replace thyroid function if the patient is allergic to Synthroid preparations
c) stimulate ^{131}I uptake in thyroid cancer and normal thyroid tissue
d) prepare the patient for thyroid surgery

18. Differentiated thyroid cancer which has lost the ability to concentrate iodine may be imaged with:

a) [^{18}F]FDG-PET
b) [^{131}I]NaI
c) [^{123}I]NaI
d) [^{131}I]MIBG

19. Patients requiring [^{131}I]NaI may be treated as outpatients if the radiation absorbed dose to the most exposed other person is less than:

a) 1 mSv (100 mrem)
b) 3 mSv (300 mrem)
c) 5 mSv (500 mrem)
d) 10 mSv (1 rem)

20. The "specific gamma ray constant" is the radiation dose:

a) in 1 cc of air at sea level at 20ºC
b) emanating from a 70 kg person
c) from an unshielded point source
d) after correcting for backscatter

21. The renal clearance half-life of ^{131}I that is not taken up by the thyroid is:

a) 2 hours in euthyroid patients with normal renal function
b) 4 hours in euthyroid patients with normal renal function
c) 6 hours in euthyroid patients with normal renal function
d) 8 hours in euthyroid patients with normal renal function

22. The renal clearance half-life of ^{131}I that is not taken up by the thyroid is:

a) 6 hours in hypothyroid patients with normal renal function
b) 12 hours in hypothyroid patients with normal renal function
c) 18 hours in hypothyroid patients with normal renal function
d) 24 hours in hypothyroid patients with normal renal function

23. The interactive web site that may be used for calculating radiation absorbed doses to others from patients treated with [^{131}I]NaI is called:

a) RADAR
b) RADSAFE
c) RADOSE
d) IODOSE

24. Case Study: AB is a 57 year-old female with early onset dementia. She currently lives in an assisted living center with a dedicated dementia program. Diagnosed with Grave's disease, she will be treated with 75 mCi of [^{131}I]NaI. Her uptake is 65%, her biological half-life is 3 days and renal function is normal. The nuclear medicine physician is seeking your advice whether to treat as an inpatient or release as an outpatient. Which of the options below would you recommend?

    a) Inpatient, estimated dose to others is greater than 500 mrem
    b) Outpatient, estimated dose to others is less than 500
    c) Inpatient, estimated dose to others greater than 100 mrem, patient unlikely to follow instructions
    d) Outpatient, estimated dose is less than 100 mrem, no patient instructions are needed.

25. Case Study: CD is a 30 year old female who received 40 mCi of [^{131}I]NaI for treatment of Grave's disease on the first on the month. Her uptake was 50%, her biological half-life was 4 days and renal function is normal. On the 25th, she calls the department very concerned since she believes she is pregnant. Which of the following facts are most relevant to this case when you discuss it with the hospital medical physicist?

    a) The estimated maternal dose at time of conception should be treated as a significant fetal hazard.

    b) Fetal thyroid tissue develops during the second trimester, at which there will be almost no residual dose.

    c) Pregnancy should be terminated and prevented for the next six months to avoid birth defects.