

# THYROID PHYSIOLOGY AND IODINE METABOLISM IN RELATION TO GOITER AND CRETINISM\*

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The thyroid gland in higher vertebrates is a highly structured gland with endocrine function. The thyroid hormones which are secreted, carry three or four Iodine atoms.

The thyroid hormones act on all body cells. In amphibia they control the complex process of metamorphosis, which includes the shedding of the tail of the tadpole and the outgrowth of the legs. In mammalian vertebrates the thyroid controls a large proportion of the oxygen consumption, of linear growth, and of development also of the central nervous system.

The basic units of the thyroid gland are the secretory follicles, small spherical sacks. In the human it has a diameter of about 1/10 - 1/2 mm. The Iodide enters the follicle cells from the blood, and the hormones  $T_3$  and  $T_4$  leave the follicle to the blood stream.

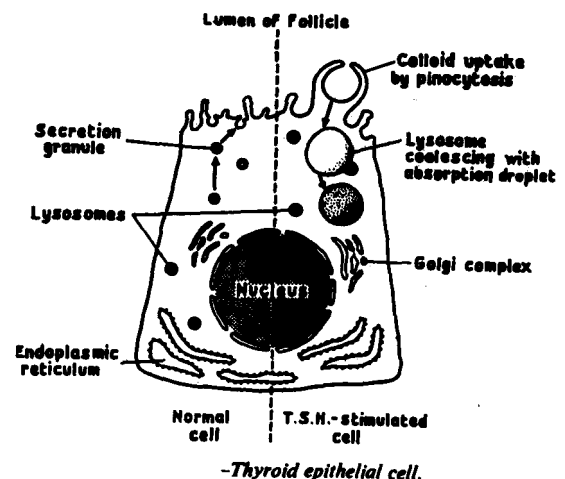
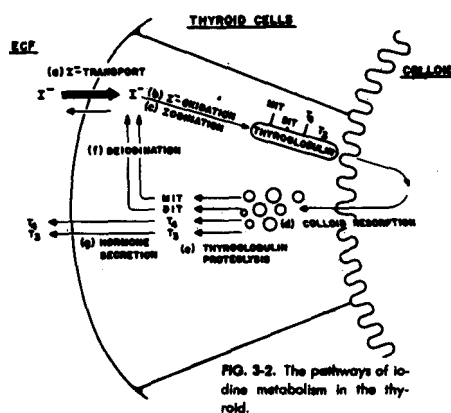
In the adult human, the thyroid gland weighs about 20 grams, is situated before the trachea, below the thyroid cartilage. It has two lobes, at the right and left, connected through the isthmus, which in most people is connected with a third lobe, the pyramidal lobe.

- The specific properties of the thyroid gland are the ability:
1. to concentrate the in-organic Iodine ion ( $I^-$ ) when it enters the cells of the thyroid. It shares this property with Salivary glands, the gastric mucosa and the mammary gland.
  2. to produce a specific protein, thyroglobulin (mol. weight 650,000), which contains 115 tyrosine molecules: it is stored in the lumen of the follicle.
  3. to fix the Iodide to the tyrosine molecules of thyroglobulin, and to condense these iodinated tyrosines to thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) and finally
  4. to split these hormones from thyroglobulin and to send them into the blood stream.

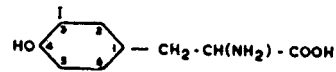
The blood flow to the thyroid gland is rich. Through a 20 gram normal thyroid gland flows 100 ml. blood per minute, or 1% of the cardiac output. The thyroid gland is only 0,03% of the body weight! The blood flow through the thyroid gland may increase to 10 times the normal flow in situations of thyrotoxicosis or endemic goiter!

\* Dibawakan pada Seminar Nasional I Gondok dan Kretin Endemik. Semarang, 18 — 20 Desember 1978.

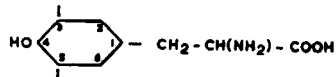
The pathway of iodine metabolism in the thyroid



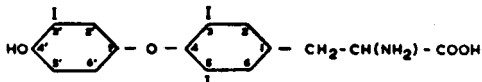
The Iodine supply of the body is of paramount importance for the normal function of the thyroid gland. More than 95% of all Iodine in the body, about 10 mg, is present in the thyroid gland. The molecular weight of thyroxine is about 770, of which 2/3 comes from the 4 large Iodine atoms! If the body does not receive enough Iodine with the food, it cannot make sufficient thyroid hormones. As stated in the beginning this has many consequences for the developing fetus, for the child, and the adolescent. The central nervous system cannot develop adequately during pregnancy which leads to mental retardation, the Corti-organ of the inner ear does not differentiate, which causes loss of hearing, the skeletal system does not differentiate or mature well, and there is also retarded growth. All these signs and symptoms are seen in the population of a severely Iodine deficient region!



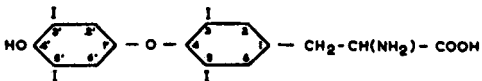
3-monoiodotyrosine



3:5-diiodotyrosine



3:5:3'-triiodothyronine  
or triiodothyronine or T<sub>3</sub>

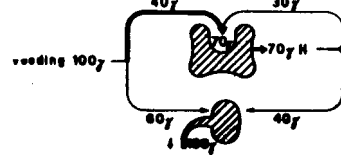


3:5:3':5'-tetraiodothyronine  
or thyroxine or T<sub>4</sub>

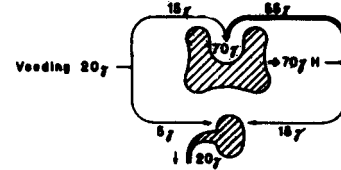
The normal daily Iodine intake should be between 100 and 200 ug per day (1 / 10 - 1/5 mg). The individual is with such an intake in balance, that means the body will lose with urine and feces an equal amount, and the body stores remain the same. If the supply or intake of iodine is much less, for instance 50 ug/day, the human body starts to use its adaptation mechanisms. It increases the size, and herewith the surface of the thyroid gland (goiter is the result) and it increases the avidity, the concentration capacity of the thyroid gland at its surface which interacts with plasma. These 2 measures, the increase of surface and with it the increase of blood flow, plus the increase of the capacity to concentrate the Iodide from the plasma, is generally enough to guarantee the gland sufficient Iodide for a normal daily hormone synthesis. We then speak of a compensated Iodine deficiency. This characterization may only be used, if under all circumstances the body is supplied with enough thyroid hormones and the plasma levels are normal. These circumstances are : during pregnancy, during lactation, during the growing period of the child, during adolescence and during adult life.

**KROPVORMING bij JODIUMDEFICIENTIE**

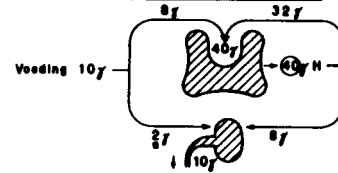
**I Normale J-stofwisseling (± 40 % halogeenoem)**



**II Gecompenseerde J-deficientie (± 80 % halogeenoem)**



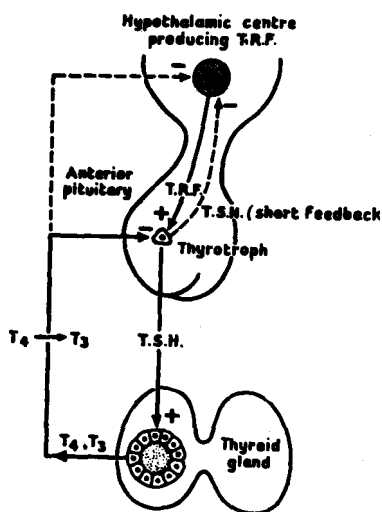
**III Onvoldoende gecompenseerde J-deficientie (80 % halogeenoem)**



It is quite clear that with a further decrease of Iodine intake, a moment comes that the thyroid does not receive enough Iodide to make sufficient hormone under all circumstances, regardless of its adaptation mechanisms. In order to understand what then happens, and what is called decompensated Iodine deficiency, requires more basic knowledge of thyroid physiology and pathophysiology.

Until now we have not given attention to two aspects of thyroid physiology. How is the thyroid function regulated, and how proceeds Iodide metabolism in the body outside the thyroid gland?

The thyroid does not function on its own, it is under control of thyrotrophic hormone, secreted by the anterior pituitary. A thyroid in an organism without a pituitary does not make thyroid hormones. The result is hypothyroidism, the result of a lack of thyroid hormones. If the machinery of the thyroid for thyroid hormone synthesis is defect (through loss of tissue, through infection as an acute, sub-acute or chronic thyroiditis, or defective enzymes) the thyroid cannot make enough thyrotrophic hormone (TSH) release. The TSH urges the thyroid to work harder, and sometimes succeeds with it. In that case the level of thyroid hormones in the blood is practically normal, but serum TSH is clearly increased. However, this mechanism may not be successful, in which case the serum thyroid hormone level will drop below normal. This is what may happen in the severely Iodine deficient individual. Here the signal is also (with a normal thyroid, which has no disease) the low serum level of thyroid hormones, in this case because there is not enough Iodine available to make the hormones. Serum TSH-level increases but the thyroid cannot make more hormone, and we find low serum T<sub>4</sub> and high serum TSH-levels.



Also a few additional data about Iodine metabolism. The thyroid has to produce about 60 80 ug T per day. It was said before that if Iodine supply decreases, the thyroid adapts by increase of size and surface, and by adding concentrating capacity. If this adaptation is sufficient, we speak of compensated Iodine deficiency. There is however also an other buffer mechanism, not yet mentioned, which can support the defence against Iodine shortage over a short time of 3-6 months. That is the Iodine reserve within the gland, which amounts to 10 mg present in thyroglobulin. This is roughly 200 times the needed daily production! Furthermore the daily thyroxine produced, is degraded during that day, and the Iodide from it is conserved and comes back to the plasma. The kidney also "clears" plasma of Iodide, just as it clears urea, chloride and many other substances. This Iodide is lost with the urine. The Iodide in the extracellular compartment therefore receives Iodide from two sides : from the food and from the breakdown of thyroxine. From this pool Iodide goes to the thyroid gland, and is Iodide lost through urine and faeces. The loss with the faeces is however a very small fraction.

In the next figure the three situations of Iodine metabolism are indicated : the normale state the compensated state and the decompensated state.

Histologically the goitrous gland initially keeps its structure and becomes hyperplastic. The cells lining the follicles are high, the colloid is decreased. After prolonged Iodine deficiency, with a continuous stimulus for growth to the gland, encapsulated adenomas develop. They are often in the resting state, and contain lots of colloid. Some may involute, other may form hemorrhagic cysts. This is finally the histological picture of the nodular goiter as we see it.

In the last scheme the findings in a population with different degree of Iodine deficiency are indicated. Goiter is the first physical abnormality which is seen in Iodine deficiency. With refined methods, using radioactive Iodine, it is possible to demonstrate the increase of the Iodide concentrating capacity before goiter is present. When the Iodine deficiency is more severe, biochemical abnormalities in the plasma will be present, and growth of children may be impaired. If the Iodine deficiency is very severe (below 25 ug

I daily intake) the fetus is at risk, and may be born with damage of the central nervous system (of which mental retardation is only a part). The noncretinuous part of the population may suffer from hypothyroidism. It is on the basis of urinary Iodine excretion that goiter endemias are classified in 3 grades :

#### Grade I :

Goiter endemias with an average urinary Iodine excretion of more than 50 ug per g creatinine. At this level, thyroid hormone supply adequate for normal mental and physical development can be anticipated.

#### Grade II :

Goiter endemias with an average urinary Iodine excretion of between 25 and 50 ug per g creatinine. In these circumstances, adequate thyroid hormone formation may be impaired. This group is at risk for hypothyroidism but not for overt cretinisms.

#### Grade III :

Goiter endemias with an average urinary Iodine excretion 25 ug per g creatinine. Endemic cretinism is a serious risk in such a population.

### THE FUNCTIONAL CONSEQUENCES OF IODINE DEFICIENCY.

INTAKE I <sub>2</sub>	COMPENSATED		DECOMPENSATED	
	BORDERLINE	DEFICIENT +	DEFICIENT ++	
CLINICAL				
Goiter	+	++	++	
Euthyroid	+	+	-	
Adeq. Linear growth	+	+?	-	
Adeq. response pregnancy	+	+ and -	-	
Cretinism	-	-	+	
Suboptimal mental development	-	?	+	

### LABORATORY

#### (NON PREGNANT)

	↑	↑ ↑	↑ ↑ or ↑
Neck uptake			
PBI	normal	average low	low
T <sub>3</sub>	normal or high	normal or high	high, normal low
TSH	normal	↑	↑

1. DJOKOMOELJANTO, R : Akibat defisiensi yodium berat. Thesis,, 1974, Semarang. Indonesia.
2. STANBURY J.B, A.M. ERMANS, B.S. HETZEL, E.A. PRETELL and A. QUERIDO. Endemic goiter and cretinism : Public health significance and prevention, WHO Choonicle, 1974, 28, 220 - 228.
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