Chapter 3.5
The thyroid and its discontents

Goal: Understand the biology and diseases of thyroid, to set up the next chapter on the origin of autoimmune diseases

The HPA axis we just studied is one of four hypothalamic-pituitary axes, or HP axes, that control pillars of life- growth, reproduction, stress, and metabolism (Fig 1). Each axis has its own circuit similar to the HPA axis (Fig 2).

We now focus on the HP-thyroid axis, or **HPT axis** for short, that controls metabolic rate. The thyroid axis is biologically fascinating, and is the target of several common diseases - especially diseases in which the body attacks itself, called autoimmune diseases.

This brief chapter is the first of a two-chapter mini-series, where we understand the origin of autoimmune diseases: what is the logic of the body attacking itself. We use the thyroid to demonstrate the biology and treatment of such diseases. We also revisit some of the principles that we studied, to understand dynamical features of these diseases such as delays between hormones and transitions between subclinical and clinical disease.

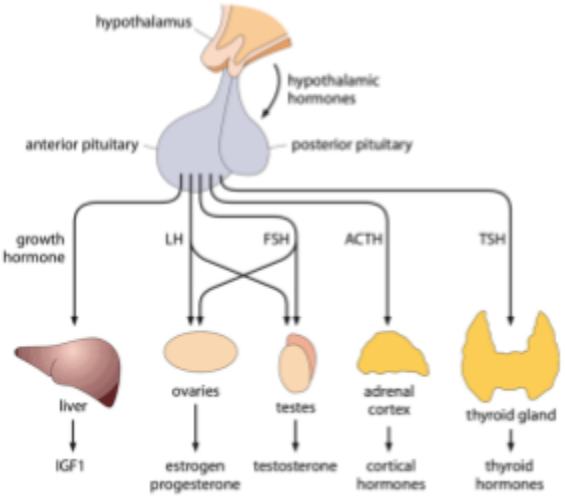

Figure 1 The HP axes regulate growth, reproduction, stress response and metabolism. Each axis has its own x1 hormones from the hypothalamus that induce second x2 hormones from the pituitary which activates secretion of the effector hormone x3 from an effector gland.

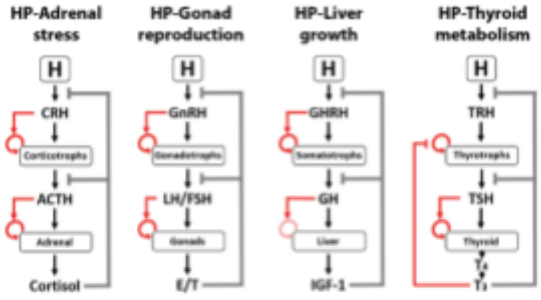

Figure 2 Each HP axis has a circuit in which the effector hormone inhibits the production of its upstream hormones (gray arrow). The hormones also act as growth factors for their downstream glands (red arrows). The HP-thyroid axis has a slightly different circuit. The names of the hormone-secreting pituitary cell types are indicated.

The HPT axis is designed to keep a steady level of thyroid hormone T4

The thyroid is a 10-gram gland at the front of our throat shaped like a butterfly (Fig. 3). It secretes thyroid hormone, T4, that goes to all cells and has far-reaching effects on the heart and on metabolism. It is the effector hormone of the HPT axis (Fig. 4). This axis, like the HPA axis, is a cascade of three hormones. The hypothalamus H secretes hormone x_1 (thyroid releasing hormone - TRH), that makes the pituitary P secrete hormone x_2 (thyroid stimulating hormone - TSH) from pituitary thyrotroph cells. TSH causes the

thyroid to secrete T4, our x_3 hormone. T4 is converted in the tissues to a more active form T3. As in the HPA axis, x_3 inhibits the production of its two upstream hormones x_2 and x_1, TSH and TRH (Fig. 4).

There is a further similarity with the HPA axis - the hormones also control the size of the glands. TSH makes the thyroid cells proliferate and grow. In fact, excessive growth of the thyroid is infamous, called goiter. It occurs when iodine, essential for making T4, is low in the diet, as in areas far from the sea which in old times lacked access to the iodine in seafood. Low T4 releases the inhibition of TSH. High TSH makes the thyroid grow up to a factor of 10, like a small melon at the throat, to try to make enough thyroid hormone.

Due to the inhibition of TSH by T4, the two hormones show an inverse relationship - when T4 is

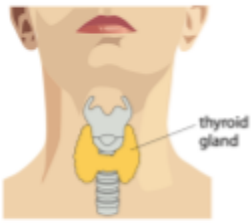

Figure 3 The thyroid is a 10g gland at the front of the throat.

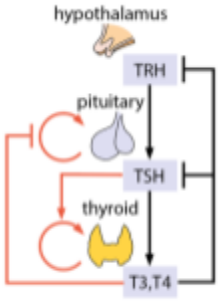

Figure 4 In the thyroid axis TSH is the growth factor for the thyroid. The effector hormones T4 and T3 inhibit the growth of pituitary cells that secrete TSH.

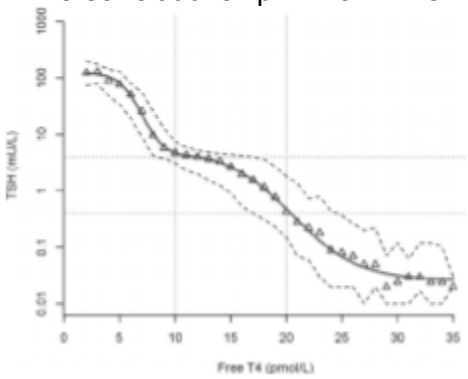

Figure 5 TSH and thyroid hormone T4 show an inverse relationship that is approximately log-linear. The normal ranges for the hormones are indicated by dashed lines (Adapted from Hadlow et.al 2013).

low TSH is high (Fig. 5 adapted from (Hadlow *et al.*, 2013)). The relation between TSH and T4 is steep, almost exponential. TSH is a sensitive indicator of problems with the thyroid. It varies by a factor of a thousand whereas T4 varies far less, with a normal range of 10-20 pmol/L. That is why TSH is such a common blood test. It can even tell if there will be future problems, even though now T4 is fine. Such abnormal TSH and normal T4 is called a subclinical disease, because it has no symptoms, but is a warning sign.

Structure-function relation in the HPT circuit

The pituitary cells that secrete TSH also have size control - the effector hormone T4 inhibits P cell growth. This is a variation on the other axes like the HPA axis - in the other axes x1 enhances P growth, instead of x3 inhibiting it. Thus, the HPA and HPT circuits differ by a single interaction arrow- the control of P growth (Fig 2).

Why this different circuit design? The answer is that the circuit structure of each axis fulfills the specific function required by that axis. The HPT axis performs homeostasis by keeping nearly constant T4 levels, whereas the HPA axis is an input-response circuit, designed to have a wide range of x_3 (cortisol) according to stress inputs. Indeed, free T4 levels in the circulation are

constant to within a factor of two. We say 'free T4' because most of T4 is bound in the blood to carrier proteins and is not active. As mentioned above, the free T4 range in the population is 10-20 pmol/L. Each healthy individual varies over time by about 50% of this range around their own personal set point.

To see how the HPT circuit achieves homeostasis, consider the equation for pituitary mass P in the HPT axis

(1) $dP/dt = P(b_p/x_3 - a_p)$

note the b_p/x_3 term which arises because x3 reduces P growth. The only way to achieve steady state $dP/dt = 0$ is for the terms in the parentheses to equal zero. This locks thyroid hormone x_3 to a steady-state equal to the ratio of P cell production and removal parameters

(2) $x_{3,st} = b_P/a_P$

This thyroid hormone steady-state is robust to changes in all other physiological parameters- reminiscent of the homeostasis of glucose levels in chapter 2.

In contrast, in the HPA axis, pituitary growth is controlled by x_1 so that $dP/dt = P(b_P x_1 - a_P)$. This equation locks x_1 to a constant steady-state $x_1 = a_P/b_P$, and keeps $x_{3,st}$ free to vary with input u, as we saw in chapter 3, as appropriate for a stress response pathway which is sensitive to the magnitude of the stressors.

Thus, circuit structure matches function.

How is thyroid hormone produced?

For our understanding of diseases, we need some details of how thyroid hormone T4 is made in the thyroid. T4 is a molecule made of two carbon hexagonal rings taken from the amino acid tyrosine (Fig. 6). Each ring has two iodines attached totaling four iodines and hence the name T4. In the cells of the body, T4 is converted to a more active form T3, so called because one of four iodines is removed by iodinase enzymes.

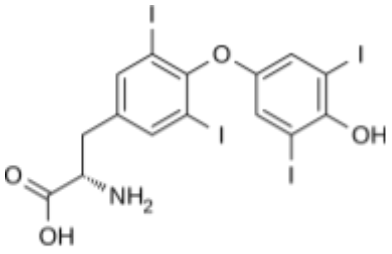

Figure 6 Thyroid hormone T4 is made of a carbon backbone bound to four iodine atoms.

T4 is made in modular chemical factories in the thyroid called the thyroid follicles (Fig. 7). Each follicle is a layer of cells called thyrocytes surrounding a spherical pore filled with colloid, with a total size of about 400 microns. The thyrocytes import iodine from the blood vessels surrounding the follicle, then export the iodine into the colloid (Fig. 8). They make huge amounts of a protein called Tg that has many tyrosines, and dump this also into the colloid. There, iodine is added to the tyrosines on Tg by an enzyme called thyroid peroxidase, or TPO. Then, the cells import the iodinated Tg back inside, break it up into small pieces, and extract the T4, and export it out of the cell into the circulation.

Remember the key proteins Tg and TPO for future use. The upstream hormone TSH increases all of the above steps, as well as the production of Tg, TPO and other transporters and enzymes involved in hormone production and secretion.

Hyperthyroidism and hypothyroidism

To understand the function of thyroid hormone T4, let's see what happens when there is too much or too little of it. Diseases with too much T4 result in **hyperthyroidism**. The heart beats fast and irregularly, which can lead to dangerous arrhythmias. Hyperthyroidism increases metabolic rate - you eat more but lose weight. Emotions and thoughts race, sometimes

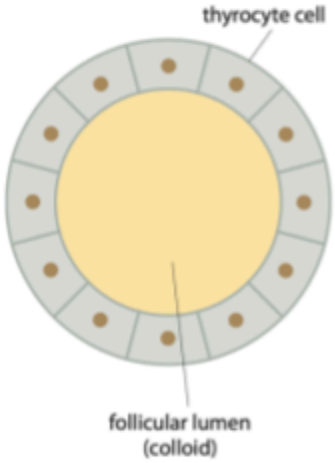

Figure 7. Thyroid hormones are produced in thyroid follicles.

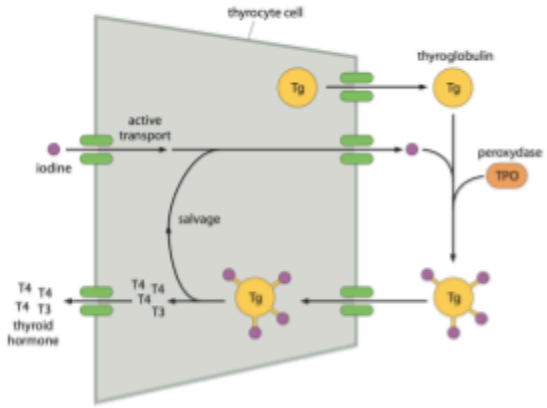

Figure 8. Thyroid hormones are produced by thyrocyte cells. The hormone precursor, thyroglobulin (Tg), is a protein with many copies of the carbon backbone of thyroid hormone, and is secreted into the lumen of the follicle. Iodine is attached to Tg in the lumen by thyroid peroxidase (TPO). Iodinated Tg is transported back to the cell and degraded to make T4 and T3 which are transported into the circulation.

resembling mania. There is a feeling of heat and sweat, due to thermogenesis. Muscles hurt. Hands might shake due to effects on the nervous system.

Opposite effects occur when thyroid hormone is too low, called **hypothyroidism**. The heart beats slowly and weakly, and you can be out of breath when climbing the stairs. You gain weight despite not eating more, with reduced appetite and constipation. Emotions tend towards depression. There is a clammy feeling of cold. In infants, hypothyroidism can lead to impaired development of the brain- that is why a TSH test at birth is so important.

Hashimoto's disease, a case of self-attack

The most common cause of hypothyroidism is Hashimoto's disease (Fig. 9) (Chaker et al., 2022). It affects about 2% of the population, primarily women. In Hashimoto's disease, white blood cells called T-cells attack and kill thyrocytes.

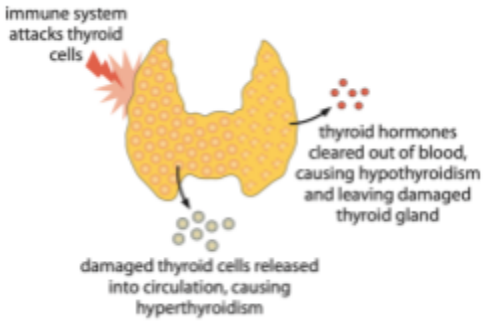

Figure 9. Hashimoto's thyroiditis, T cells destroy thyrocytes and eventually destroy so much of the thyroid that thyroid hormone levels drop below their normal range - a serious condition known as hypothyroidism.

The T-cells normally attack virus infected cells, not healthy cells of the body. Unfortunately, in Hashimotos, T-cells attack healthy thyrocytes and damage the thyroid. More in the next lecture.

The antigens recognized by T-cells in Hashimotos are pieces of the Tg and TPO enzymes discussed above. The T-cells also activate B-cells to make antibodies against Tg and TPO. The antibodies participate in damaging the thyroid. Hashimotos is clinically identified by anti-Tg and anti-TPO antibodies in the blood.

Sometimes, early stages of Hashimoto's cause T4 to spill from destroyed cells, causing hyperthyroidism. This is soon followed by hypothyroidism as the thyroid is destroyed.

Hashimoto's disease is treated by supplying thyroid hormone in pills. The pills are taken for life since the autoimmune attack never stops (though it can come in waves). Most people live fine with these pills. However, a small percentage of the population has problems adjusting the dose. This causes problems for millions of people.

TSH shows a delay after Hashimoto's is treated

When Hashimoto's is treated by T4 pills at the proper dose, T4 recovers to its normal range. TSH however remains high for 6 weeks after T4 normalizes (Fig. 10). This delay is usually not explained in endocrinology textbooks. It cannot be explained by the hormone lifetimes which are much faster. This delay makes it difficult to adjust treatment dose and stabilize patients based on TSH blood tests.

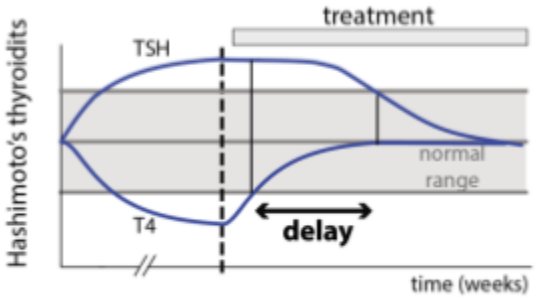

Figure 10. Delay in the treatment of Hashimoto's thyroiditis. When treated by pills that supply thyroid hormones, the levels of thyroid hormone T4 return to normal. TSH returns to normal only after a delay of about 6 weeks relative to T4.

The origin of the delay cannot be understood unless we take the changes of gland masses into account. When thyroid hormone production is compromised by autoimmune attack of the thyroid, there is less T4. Since T4 inhibits pituitary growth, low T4 lifts this inhibition. The pituitary functional mass grows, to make more TSH to stimulate the thyroid and compensate for the killing. When the disease is treated, by taking thyroid hormone pills, it takes the enlarged

pituitary 6 weeks to shrink back to its normal size. As a result, it takes TSH 6 weeks to return to baseline (Korem Kohanim et al., 2022).

Subclinical Hashimotos is due to dynamical compensation

In fact, the disease can go quietly for decades with no symptoms, long before T4 levels drop below normal (Fig. 11). In this **subclinical** stage, thyroid cells are killed by the immune system. TSH is high but T4 is normal.

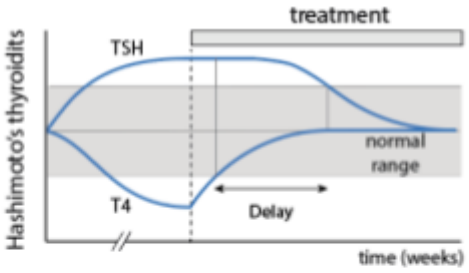

Figure 11 Subclinical Hashimoto's thyroiditis occurs when TSH is higher than normal but thyroid hormones are normal. Thyroid hormone is maintained in the normal range due to dynamic compensation in which the pituitary cells that secrete TSH grow in effective mass, producing excessTSH to compensate for autoimmune killing of the thyroid. When the pituitary cell mass approaches its carrying capacity, this compensation maxes out, and thyroid hormones drop below normal, instigating clinical Hashimoto's thyroiditis.

The origin of the subclinical stage is the dynamical compensation effect that we discussed before. The pituitary cell total mass grows so that more TSH is secreted, to precisely compensate for the killing of thyrocytes.

To understand the subclinical stage in terms of equations, we can build on our experience with the HPA axis. The growth of thyroid mass T is stimulated by TSH, denoted x2, so that $dT/dt = T(b_T x2 - a_T)$. The steady state of TSH, $x2 = a_T/b_T$, is proportional to the removal rate of thyroid cells, a_T. Since autoimmune killing increases thyrocyte removal rate a_T, it causes the high TSH levels observed in Hashimoto's thyroiditis. The pituitary mass grows to supply this extra TSH. However, the level of thyroid hormone, denoted x3, is kept constant by the previously mentioned equation for the pituitary mass, $dP/dt = P(b_P/x3 - a_P)$, so that thyroid hormone is normal $T4 = x3 = a_P/b_P$. Clinically, doctors recommend a followup test to see if T4 levels fall below their normal range.

But according to law 2, biological processes saturate. If the killing rate of the autoimmune disease exceeds a threshold, the pituitary mass approaches its carrying capacity. Compensation by the pituitary maxes out and TSH reaches its maximal level. Any rise in autoimmune killing rate now causes the thyroid hormone x_3 to drop below its healthy range. Clinical hypothyroidism emerges. Many people therefore rely on compensation by gland mass changes for health.

Hyperthyroidism due to toxic nodules: a case of a hypersensing mutant

We now turn to hyperthyroidism, too much T4. One major cause is a batch of growing cells in the thyroid that form a nodule that secretes too much thyroid hormone T4 (Fig. 12). These nodules can be imaged by ultrasound, felt by touch, and seen to be active in secreting T4 by a radioactive iodine scan. Since they show up on the scan, they are called 'hot nodules' or **toxic nodules**. They occur in about 1% of the population, primarily at old age.

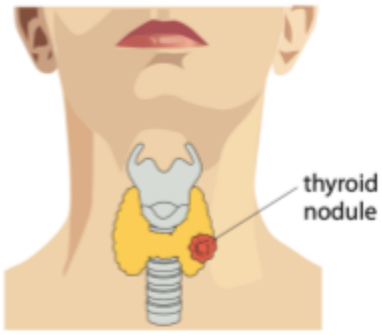

Figure 12. A thyroid nodule is a growth in which a mutant thyrocyte cell proliferates excessively.

There are also 'cold nodules' that do not secrete T4. Cold nodules are 10 times more likely than hot nodules to become cancerous (to spread to other body parts to form metastases). Hot nodules are very rarely cancerous.

Toxic nodules are an example of a principle we have seen before. The thyroid cells are controlled by the grow-and-secrete feedback circuit in which a signal, TSH, makes the cells both secrete more hormone and to proliferate. The circuit is analogous to the beta cell circuit (Fig 13).

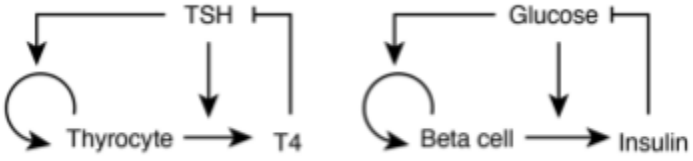

Figure 13 The thyrocytes are regulated by a secrete-and-grow circuit analogous to beta cells.

This circuit has a fragility as we have seen: Mis-sensing mutant cells that "think" there is too much signal can divide and form a nodule that secretes too much hormone.

This is exactly what happens in a toxic thyroid nodule. The nodule cells are all copies (a clone) of an original mutant cell with a mutation, usually in the TSH receptor, that makes it more sensitive to TSH. There are at least 50 such known mutations in the TSH receptor gene that cause toxic nodules. The mutant cell does what it thinks is right- it is misinformed by the mutant receptor to think that TSH is high so that it must divide and secrete more thyroid hormone. The mutant cell proliferates and over many years grows to a toxic nodule that causes hyperthyroidism.

Often the treatment of toxic nodules is their surgical removal.

It is interesting to consider why the thyroid does not have a biphasic mutant resistance mechanism like beta cells, where cells that sense too much glucose kill themselves. Recall that this effect, called glucotoxicity, gives strong missensing mutants a selective disadvantage.

Why does the thyroid lack a biphasic effect, something we might call TSH-toxicity? It would be nice if a cell that senses high TSH would kill itself to avoid toxic nodules. However, unlike beta cells, the signal in the thyroid axis, TSH, varies over a 1000-fold range to compensate for physiological variation, such as iodine levels in the nutrition which can vary over at least a 100-fold range. If there was TSH toxicity, thyroid cells would kill themselves if iodine is low,

which would be lethal. Blood glucose has a much smaller range of variation and is thus a good candidate for biphasic regulation. The thyroid is thus prevented from using a TSH-toxicity due to its need for extensive compensation.

In the next chapter we will see how the need for mutant resistance can explain the physiological role of autoimmune attack of the thyroid.

Why are there autoimmune diseases of hormone glands?

Why is the thyroid attacked by the body? Why risk 2% of the population with a potentially deadly disease? Hashoimotos thyroiditis was deadly before medicine turned it into a curable disease. The same question for beta cells, where type-1 diabetes is an autoimmune attack on beta cells that was a death sentence to about 1% of children before the advent of insulin treatment.

Also, why these particular cell types and not others? For example, right next to the beta cells are alpha cells that produce glucagon. Why is there no autoimmune disease that attacks alpha cells?

If you want to consider some answers, read on.

Further reading:

Korem Kohanim, Y., Milo, T., Raz, M., Karin, O., Bar, A., Mayo, A., … Alon, U. (2022). Dynamics of thyroid diseases and thyroid-axis gland masses. *Molecular Systems Biology*, *18*(8), e10919. https://doi.org/10.15252/msb.202210919

Chatzitomaris, A., Hoermann, R., Midgley, J.E., Hering, S., Urban, A., Dietrich, B., Abood, A., Klein, H.H., and Dietrich, J.W. (2017). Thyroid Allostasis–Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming. Front. Endocrinol. *8*.

Chaker, L., Razvi, S., Bensenor, I. M., Azizi, F., Pearce, E. N., & Peeters, R. P. (2022). Hypothyroidism. *Nature Reviews Disease Primers 2022 8:1*, *8*(1), 1–17. https://doi.org/10.1038/s41572-022-00357-7

Hadlow, N.C. *et al.* (2013) 'The Relationship Between TSH and Free T4 in a Large Population Is Complex and Nonlinear and Differs by Age and Sex', *The Journal of Clinical Endocrinology & Metabolism*, 98(7), pp. 2936–2943. Available at: https://doi.org/10.1210/jc.2012-4223.

Exercises:

3.5.1 A model for compensation in the thyroid axis

(a) Write equations for the thyroid axis, identical to the HPA axis except that x3 inhibits P growth instead of x1 enhancing P growth (Korem Kohanim, 2022) .
(b) What is the steady state of the three hormones? Compare this to the HPA axis.
(c) When iodine is lacking, the thyroid is less effective at making thyroid hormone, x3. As a result, there is compensation. Model low iodine by reducing the x3 synthesis rate parameter q3. How do the hormones x1, x2 and x3 change as a function of q3? How do the gland sizes change? Why is there often an enlarged thyroid gland in regions of low iodine, a condition called Goiter?
(d) Why is the hormone x2, called TSH, considered an excellent clinical blood test for thyroid problems?

3.5.2 Graves disease:

Graves disease is an autoimmune disease that causes hyperthyroidism in about 1% of the population, usually at middle age. In Graves disease the body produces antibodies that activate the TSH receptor, mimicking TSH. As a result, the thyroid produces more thyroid hormones.

(a) Use the thyroid mode of exercise 3.5.1 to model Graves disease, by changing x2, the hormone TSH, to x2+Ab, where Ab are the activating auto-antibodies.
(b) Plot the levels of the hormones and seize of the glands as a function of Ab.
(c) Explain the transition from subclinical hyperthyroidism to clinical hyperthyroidism. What happens to the pituitary cell mass P at the transition point (Korem Kohanim, 2022)?