Treatment of Hypothyroidism- A Different View
The Deiodinase Story

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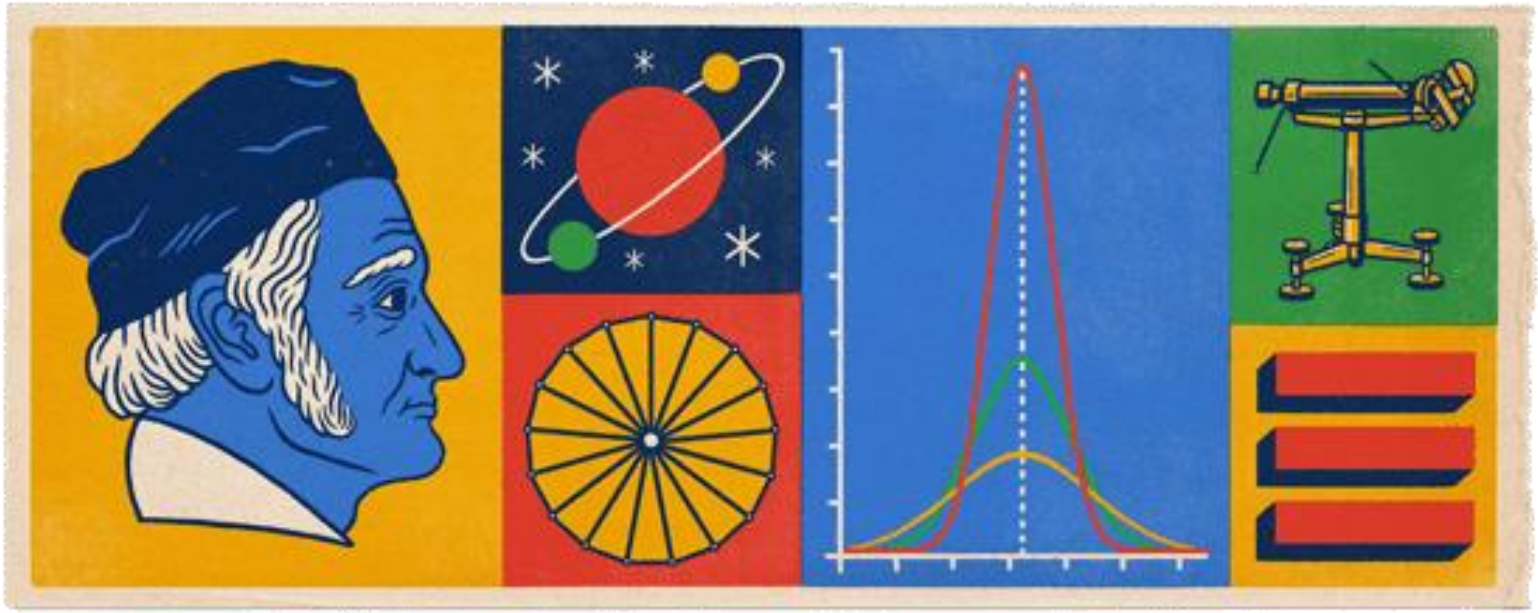


Johann Carl Friedrich Gauss b. 30.04.1777

The Early Days of Thyroidology

- 1850-1883: Gradual realization that cretinism and myxedema were connected to the lack of function or absence of the thyroid (gland, Semon 1883)

Age 21

28

32

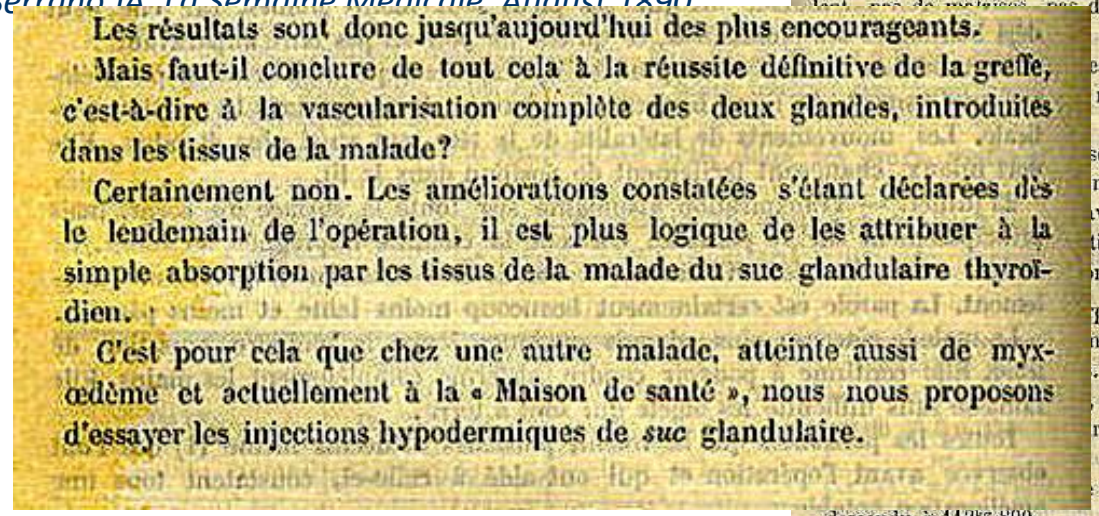
- First described patient with evolving “myxedema” 1878

William. M. Ord, “On myxoedema, a term proposed to be applied to an essential condition in the ‘cretinoid’ affection occasionally observed in middle-aged women,” Medico-Chirurgical Transactions, vol. 61, pp. 57–74, 1878.

The Early Days of Thyroidology

- Myxedema invariably fatal within 10 years

Bettencourt R, Serrano JA. La Semaine Médicale. August 1890

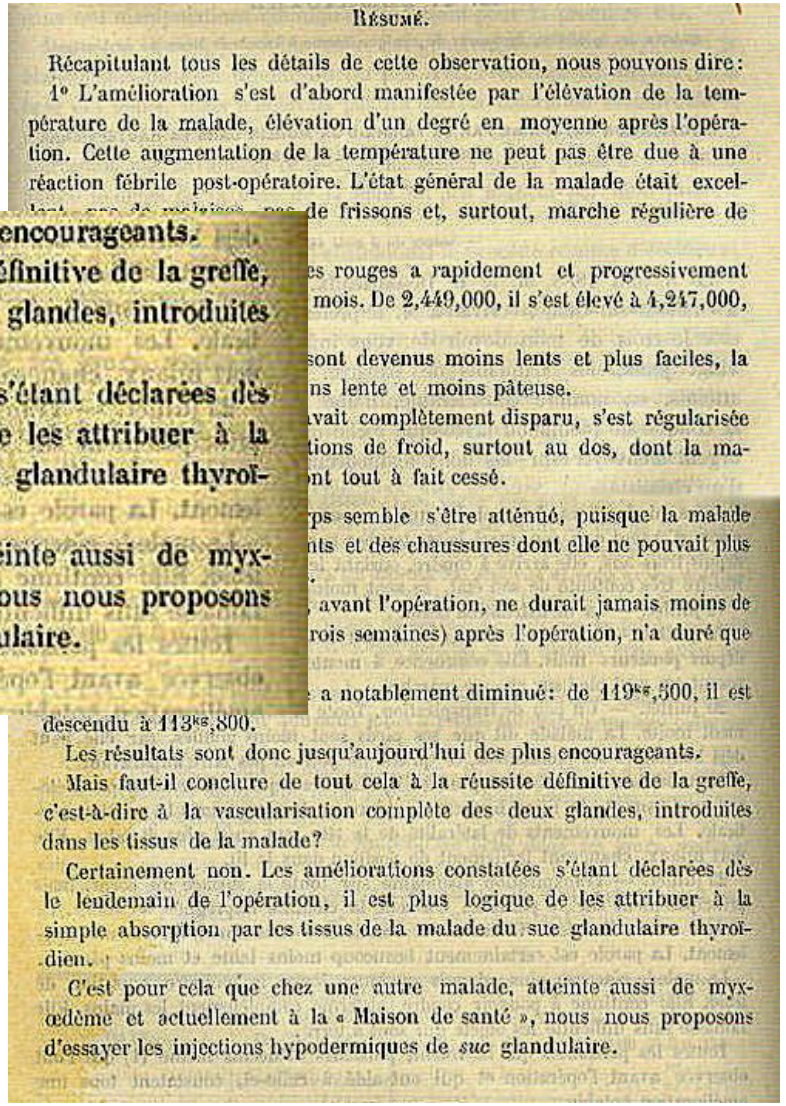


Les résultats sont donc jusqu'aujourd'hui des plus encourageants.

Mais faut-il conclure de tout cela à la réussite définitive de la greffe, c'est-à-dire à la vascularisation complète des deux glandes, introduites dans les tissus de la malade?

Certainement non. Les améliorations constatées s'étant déclarées dès le lendemain de l'opération, il est plus logique de les attribuer à la simple absorption par les tissus de la malade du suc glandulaire thyroïdien.

C'est pour cela que chez une autre malade, atteinte aussi de myxœdème et actuellement à la « Maison de santé », nous nous proposons d'essayer les injections hypodermiques de *suc* glandulaire.



Résumé.

Récapitulant tous les détails de cette observation, nous pouvons dire:

1° L'amélioration s'est d'abord manifestée par l'élévation de la température de la malade, élévation d'un degré en moyenne après l'opération. Cette augmentation de la température ne peut pas être due à une réaction fébrile post-opératoire. L'état général de la malade était excel-

de frissons et, surtout, marche régulière de

es rouges a rapidement et progressivement
mois. De 2,449,000, il s'est élevé à 4,247,000,

sont devenus moins lents et plus faciles, la
ns lente et moins pâteuse.

vait complètement disparu, s'est régularisée
tions de froid, surtout au dos, dont la ma-
nt tout à fait cessé.

rps semble s'être atténué, puisque la malade
nts et des chaussures dont elle ne pouvait plus

avant l'opération, ne durait jamais moins de
rois semaines) après l'opération, n'a duré que

a notablement diminué: de 119ᵏᵍ,500, il est descendu à 113ᵏᵍ,800.

Les résultats sont donc jusqu'aujourd'hui des plus encourageants.

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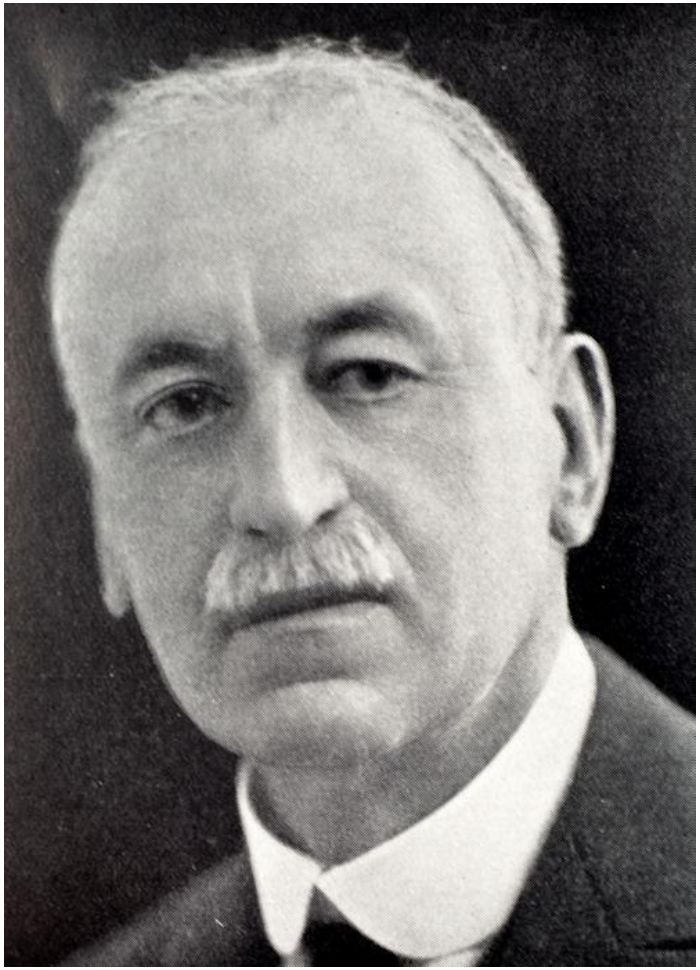
The Early Days of Thyroidology



NOTE ON THE TREATMENT OF MYXŒDEMA BY HYPODERMIC INJECTIONS OF AN EXTRACT OF THE THYROID GLAND OF A SHEEP.

Read in the Section of Therapeutics at the Annual Meeting of the British Medical Association held in Bournemouth, July, 1891.

By GEORGE R. MURRAY, B.A., M.B.Camb., M.R.C.P.Lond.,
Newcastle-on-Tyne.

Myxœdema has until recently been considered an incurable disease. Since the pathology of this remarkable condition, however, has become more fully understood, hopes of the possibility of greatly relieving the symptoms, if not of curing the disease entirely, have been entertained. The observations of the symptoms which followed the removal of the thyroid gland in man made by Professor Kocher, of Berne, and the results of the experimental removal of the gland in monkeys obtained by Mr. Victor Horsley [1] have firmly established the view that this disease is due to the loss of function of the thyroid gland. It was found by Dr. von Eiselsberg that if the thyroid gland was successfully transplanted from the neck of an animal to some other part of the body, it was capable of continuing its functions, and so preventing the onset of the symptoms which would otherwise have followed its removal from the neck. Mr. Horsley then suggested that grafting a healthy sheep's thyroid gland into a patient suffering from myxœdema should be tried as a means of arresting the

BMJ 1891

SIXTIETH ANNUAL MEETING
OF THE
BRITISH MEDICAL ASSOCIATION
Held in NOTTINGHAM, July 26th, 27th, 28th, and 29th.

PROCEEDINGS OF THE SECTIONS.

PATHOLOGY.

Professor Victor Horsley, M.B., F.R.C.S., F.R.S., President.

THE PATHOLOGY AND TREATMENT OF MYXŒDEMA.

REMARKS ON THE TREATMENT OF MYXŒDEMA WITH THYROID JUICE, WITH NOTES OF FOUR CASES.

By G. R. MURRAY, B.A., M.B.Cantab., M.R.C.P.Lond.,
Lecturer on Bacteriology and Comparative Pathology in the University of Durham College of Medicine; Pathologist to the Hospital for Sick Children, Newcastle-on-Tyne.

Professor Victor Horsley has so conclusively shown by his own original work[1] and by the experimental and clinical evidence brought forward in a recent paper[2] that myxœdema is due to the loss of function of the thyroid gland that further evidence in support of this view may seem scarcely to be necessary. The evidence which I wish to bring before you has however a double interest, for it both supports this view of the causation of myxœdema and shows how, by a practical application of this knowledge, the condition of patients suffering from this disease can be considerably improved.

M. H. A., October, 1891. Before treatment.

In health the thyroid gland plays an important part in keeping the blood in a normal condition and in maintaining the natural metabolism of the tissues. This is shown by the changes which take place when it is lost and myxœdema comes on. This function of the thyroid gland is probably carried on to a considerable extent by means of its secretion, which is carried into the blood.

If this really be so, we ought to be able in a case of myxœdema to remove those symptoms which are due to the loss of this secretion only, by introducing the secretion from a healthy thyroid gland into the body of the patient in such a way that it can be slowly absorbed by the lymphatics and carried into the circulation as in health.

In the case of animals, G. Vassale[3] and E. Gley[4] have both shown that injections of thyroid extract remove the acute symptoms which follow thyroidectomy in dogs. Brown-Séquard and d'Arsonval,[5] reasoning from these results, suggested last year that injections of thyroid extract would do good in myxœdema. Previously to this, however, I had tried the effect of injections of an extract of the thyroid gland of a sheep in a well-marked case of myxœdema[6] with such satisfactory results that other cases have been treated in the same way. For the injections an extract of the thyroid gland of a sheep has been prepared freshly for me each week by Messrs. Brady and Martin, of Newcastle, in the following manner: The thyroid glands are removed from several sheep just after they have been killed. Each lobe is minced and then bruised in a mortar. For each lobe employed 1 c.c. of glycerine and 1 c.c. of a 0.5 per cent. solution of carbolic acid in boiled distilled water is added. The mixture is allowed to stand for twelve hours, and then squeezed through a cloth in a press so as to obtain as much liquid as possible from the mixture. All the apparatus used in the preparation is previously cleansed by boiling water and 1 in 20 carbolic acid solution.

In future the manufacturers are going to sterilise the extract by pressure at ordinary temperatures by means of the liquefied carbonic acid apparatus used by M. d'Arsonval.[7] This will minimise the danger of causing local inflammation and suppuration.

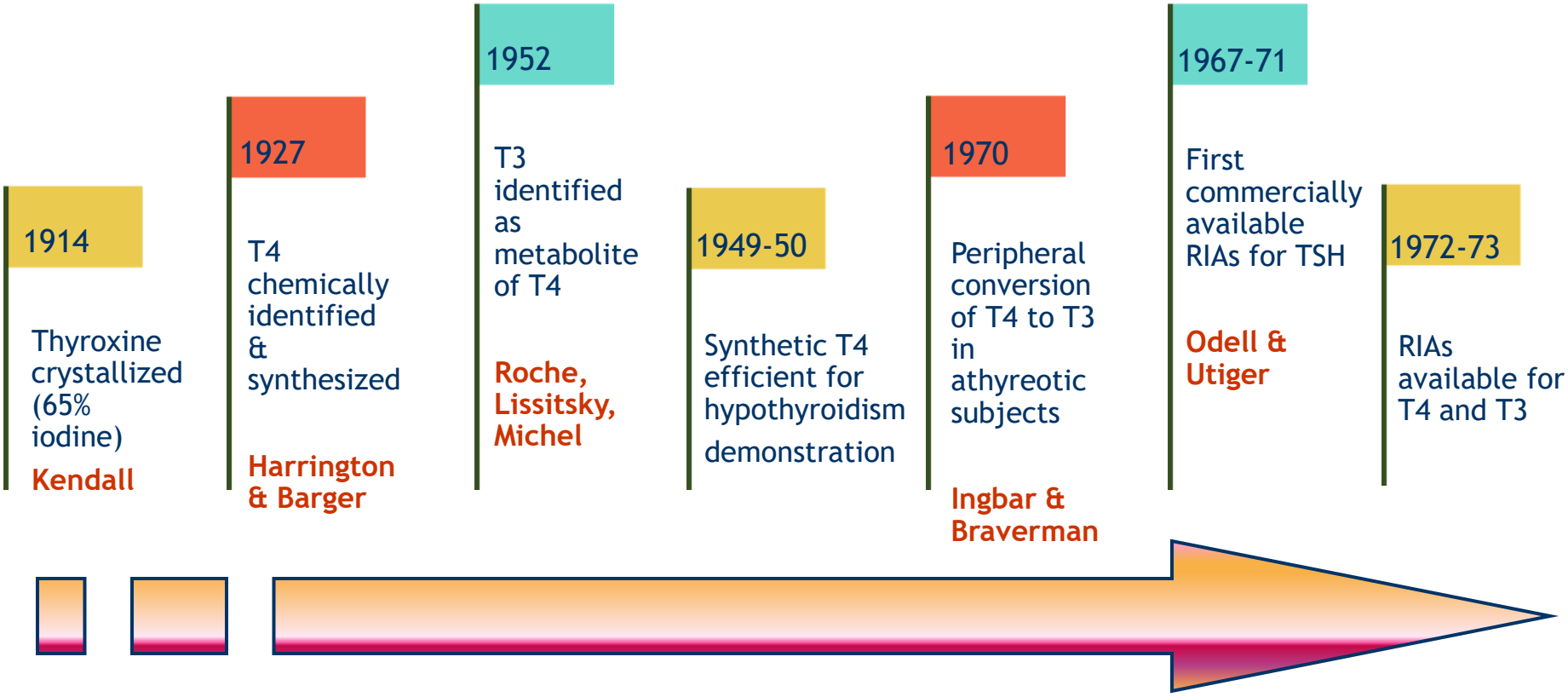
As a rule, ℥xxv of the extract have been injected with antiseptic precautions beneath the skin of the interscapular region once a week. In some cases it may be better to give a smaller injection of ℥x to ℥xv more frequently. The injection is given slowly, so that five minutes are occupied in injecting ℥xxv. This is advisable, as occasionally some peculiar symptoms have immediately followed a rapid injection. These were flushing, nausea, and stabbing pain in the lumbar region. Once there was also loss of consciousness and general tonic muscular spasm for a few seconds. When given slowly, the injection can be stopped if the patient begins to flush. No pressure should be made on the seat of injection, as it seems probable that these symptoms are due to a too rapid entrance of the extract into the circulation.

M. H. A., June, 1892. After treatment for seven months.

Case I.—This case, related more fully in my last paper, was a woman of 46, who had suffered from myxœdema for four or five years. There was well marked swelling of the face and hands, dry skin without perspiration, subnormal temperature, languor, and slow speech. After treatment for three months the swelling had greatly diminished, the natural expression of the face returned, the skin became moist, perspiration returned, the temperature rose, and there was marked improvement in the mental and bodily activity. After four months a considerable quantity of new hair had appeared on the head and had grown an inch in length. In this case this improvement, with the exception of the temperature, has been maintained for ten months by means of injections of ℥xxv of the

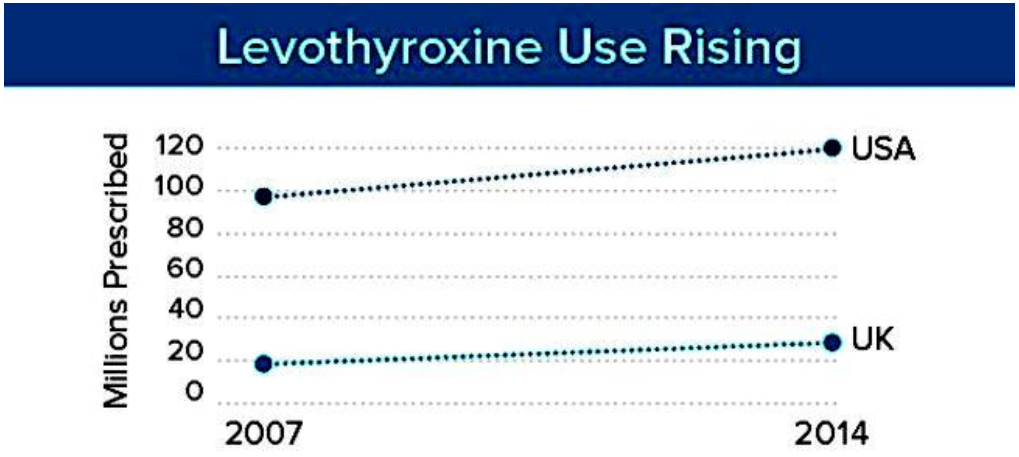
[1] *Brown Lectures*, 1884.
[2] British Medical Journal, January 30th, 1892.
[3] *Rivista sperim. di Freniatria*, vol. xiv, fasc. iv, 1890, p. 439.
[4] *Comptes Rendus de la Soc. de Biol.*, April 24th, 1891, p. 260.
[5] *Archives de Physiologie*, No 3, July, 1891.
[6] British Medical Journal, October 10th, 1891, p. 786.
[7] *Archives de Physiologie*, No. 3, July, 1891.

The Early Days of Thyroidology-Timeline



Treatment of Hypothyroidism Evolution

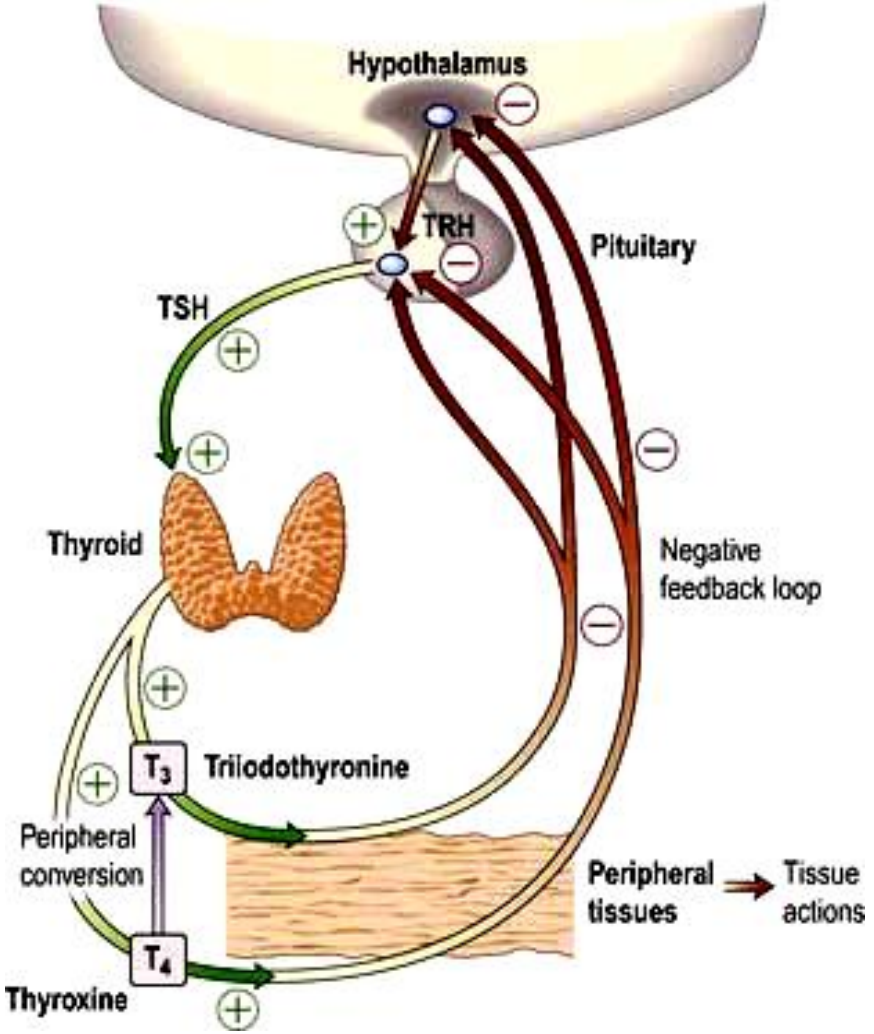
- Dessicated thyroid mainstay Rx 1890s-mid 1970s
- RMR and PBI used in the pre-RIA era
- Concerns about dessicated thyroid
  - Inconsistencies in potency
  - Short shelf life
  - Sensitivity to humidity
- 1977-LT4 monotherapy new standard of care

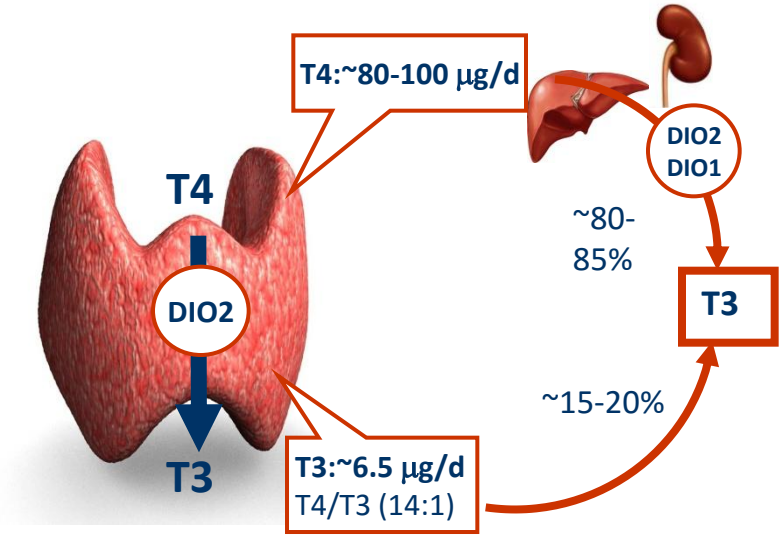


Source: *Lancet Diabetes Endocrinol.* Published online October 28, 2016.

- Treatment aim: normalization of TSH

The HPT Axis-The Simplistic View

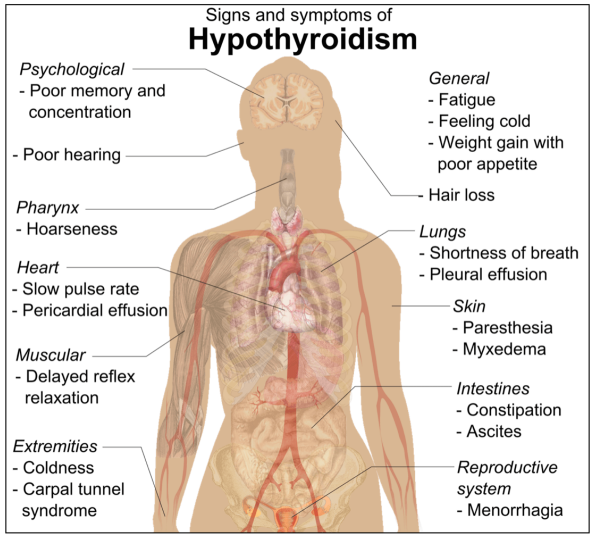




- Free T3 (0.4% of TT3) involved in feedback regulation
- Affinity of T3 for TR~10 times higher than T4

Treatment of Hypothyroidism Evolution

- Lower doses of T4 to normalize TSH (100-200) than to normalize PBI and RMR
- 10-15% of hypothyroid patients with normal TSH still symptomatic
- Normal TSH but T3/T4↓, some with frankly low T3 (particularly after Thyre$_x$)



- Some patients need to have suppressed TSH to get relief
- Some patients improve from combined therapy or dessicated thyroid-DTE

Challenges to the “Physiology” of LT4 MonoRx

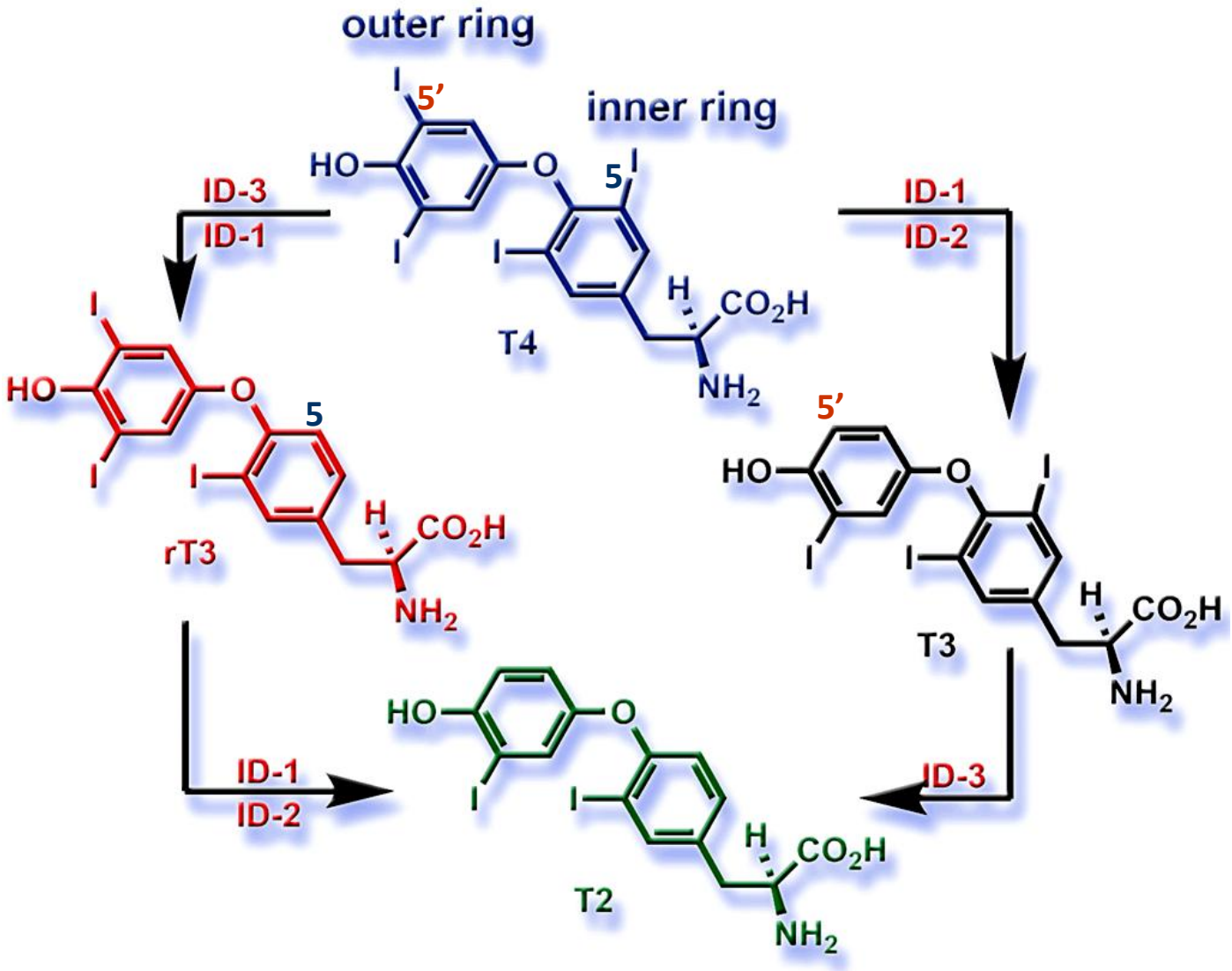
- Thyroidectomized rats on T4 Rx, have normal TSH with low tissue T3
- These levels can be normalized with concomitant T3 administration

  Escobar-Morreale HF, et al. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. J. Clin. Invest. 1995;96:2828

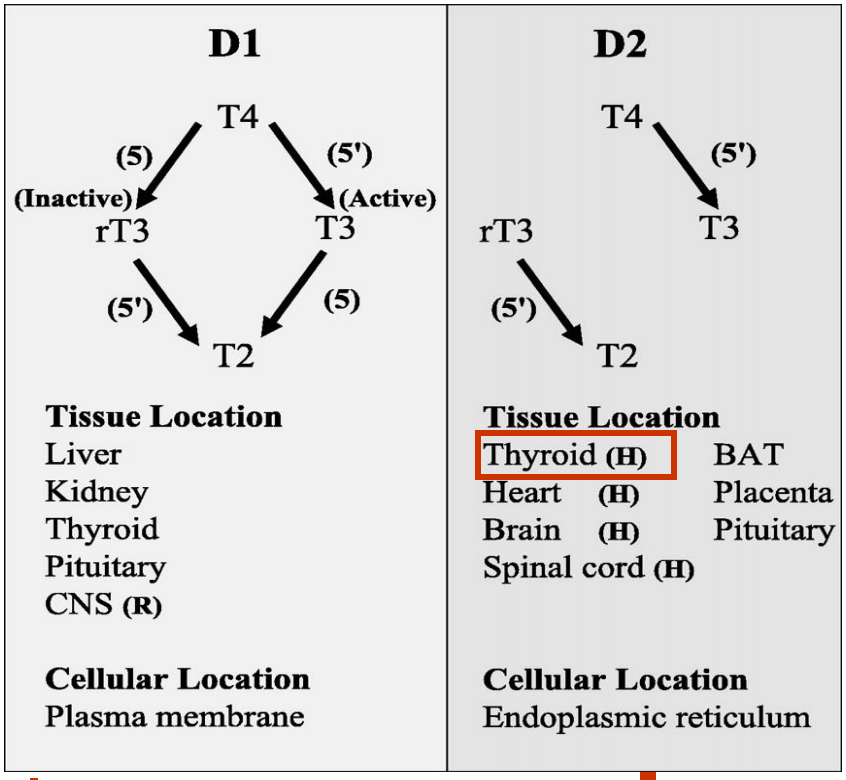
Evolving Understanding of the HPT Axis

- **Deiodinases**
- Thyroid hormone transporters (MCT8, OATPs, LATs)
- Binding proteins genetic defects
- Non genomic effects of thyroid hormones
- TR genetic variations, and tissue distribution
- Co-activators, co-repressors
- Thyronamines
- Drugs

Deiodinases-Selenoproteins



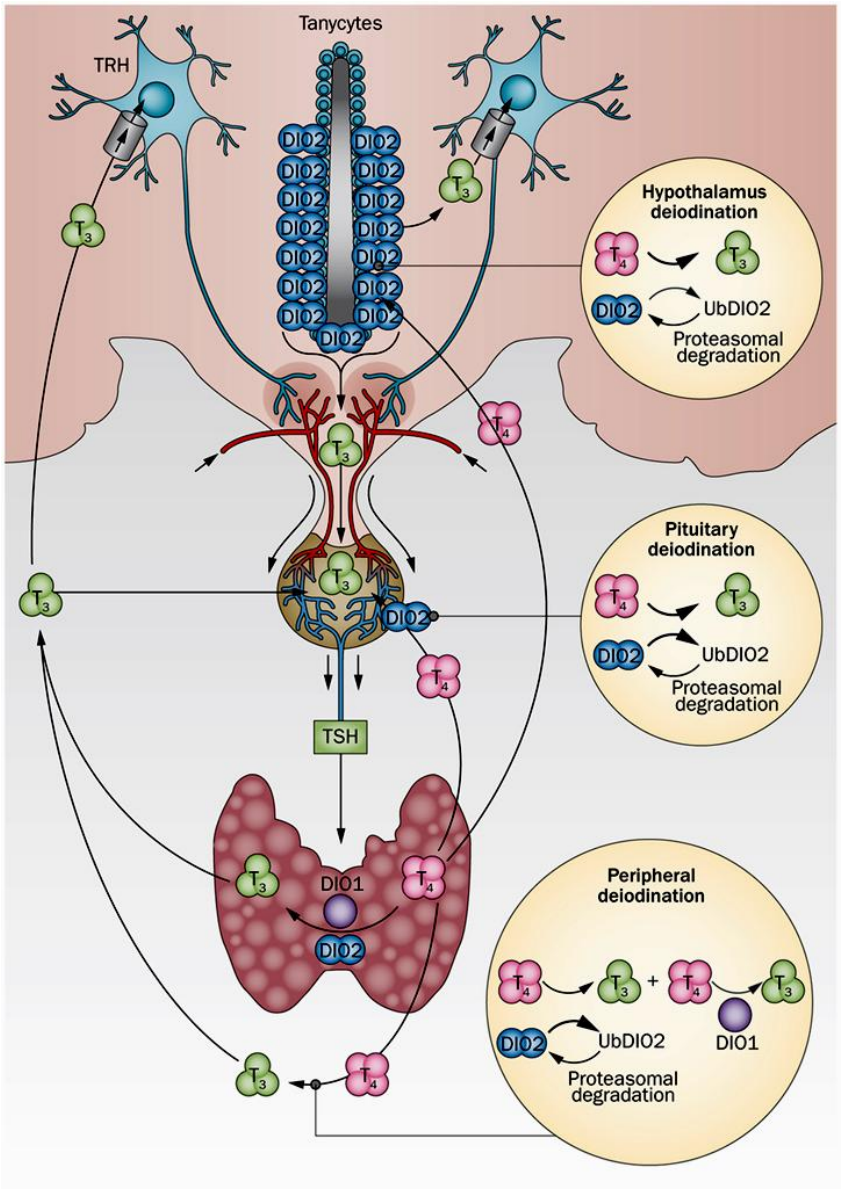
Deiodinases Expression and Regulation



~15% of plasma T3

- ~70% of plasma T3 from extrathyroidal T4 conversion
- Contributes to intracellular T3
- Induced in hypothyroidism
- **Inactivated by ubiquitination**
- **Role of polymorphisms**

Hypothalamus DIO2 is Resistant to Ubiquitination



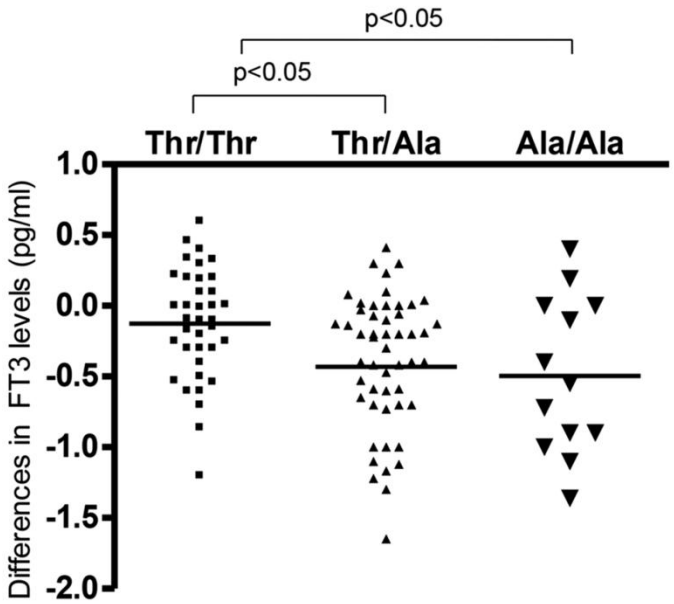
Differences in hypothalamic type 2 deiodinase explain localized sensitivity to thyroxine.
Werneck de Castro et al. J Clin Invest. 2015; 125:769

Explains normal or suppressed TSH in face of low plasma or tissue T3 under T4 monotherapy

Potential Role for DIO2 Thr92Ala Polymorphism

- Common allele (~50% Thr/Ala, ~16% Ala/Ala)
- Higher T4 to suppress TSH after Sx in DTC *(Torlontano et al JCEM, 2009, n=190)*
- Lower QoL on T4 Rx, improvement on T4+T3 in hypothyroid subjects *(Panicker et al, JCEM 2009, n=552)*
- Reduced T3 after surgery in Ala subjects at unchanged TSH (~0.9) and lower DIO2 activity in transfected cells *(Castagna, JCEM 2017, n=140)*

	Pre-surgical FT3 (pg/ml)	Post-surgical FT3 (pg/ml)	p
WT			
Mean±SD	3.2±0.35	3.1±0.36	
Range	2.4-3.9	2.6-4.1	0.097
Median	3.2	3.1	
Thr/Ala			
Mean±SD	3.4±0.52	3.0±0.28	
Range	2.7-5.4	2.5-3.9	<0.0001
Median	3.3	2.9	
Ala/Ala			
Mean±SD	3.4±0.37	2.9±0.34	
Range	2.9-4.2	2.5-3.6	0.01
Median	3.4	2.9	



Role of Thyroid DIO2 in HPT Axis Regulation

Role of Thyroid DIO2 in HPT Axis Regulation

OPEN ACCESS Freely available online

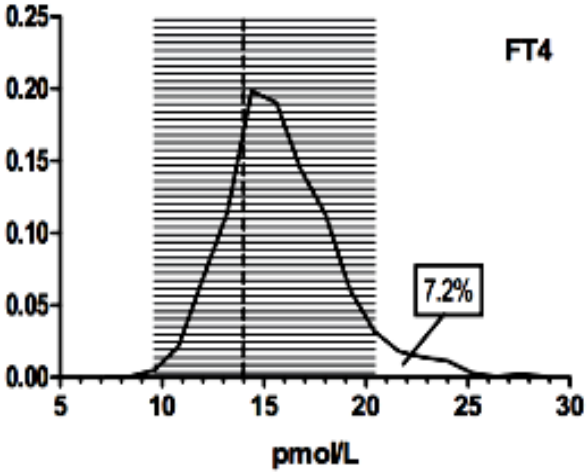
PLoS one

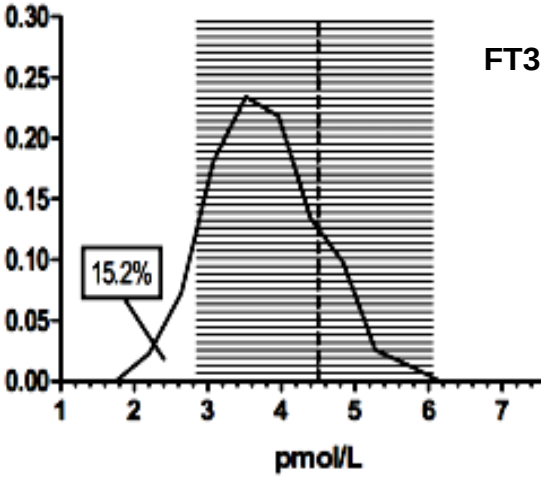
Levothyroxine Monotherapy Cannot Guarantee Euthyroidism in All Athyreotic Patients

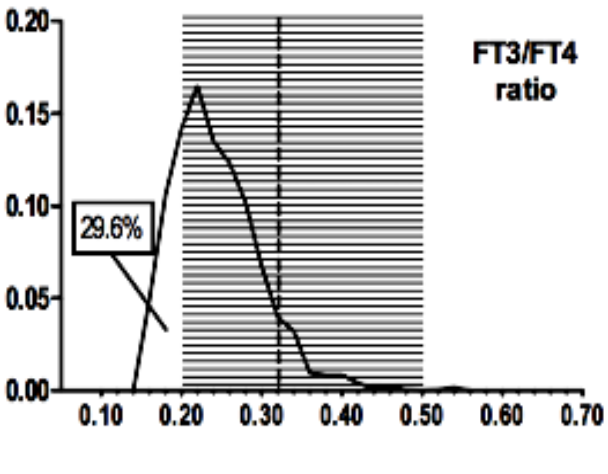
Damiano Gullo*, Adele Latina, Francesco Frasca, Rosario Le Moli, Gabriella Pellegriti, Riccardo Vigneri

Endocrine Unit, Department of Clinical and Molecular Biomedicine, University of Catania Medical School, Garibaldi-Nesima Hospital, Catania, Italy

	F/M	N	Age	TSH	FT4	FT3	FT3/FT4	L-T4 (μg/kg/d)
Ctrls	4.9:1	**3875**	49	1.4 (0.9-2.1)	13.8 (12-15.4)	4.47 (3.9-4.9)	0.32 (0.27-0.37)	
T4 treated	5.4:1	**1811**	51	1.2 (0.7-2.2)	15.4 (14.2-17.6)	3.7 (3.2-4.3)	0.24 (0.2-0.28)	1.59 (1.36-1.86)







Role of Thyroid DIO2 in HPT Axis Regulation

Effect of the presence of remnant thyroid tissue on the serum thyroid hormone balance in thyroidectomized patients

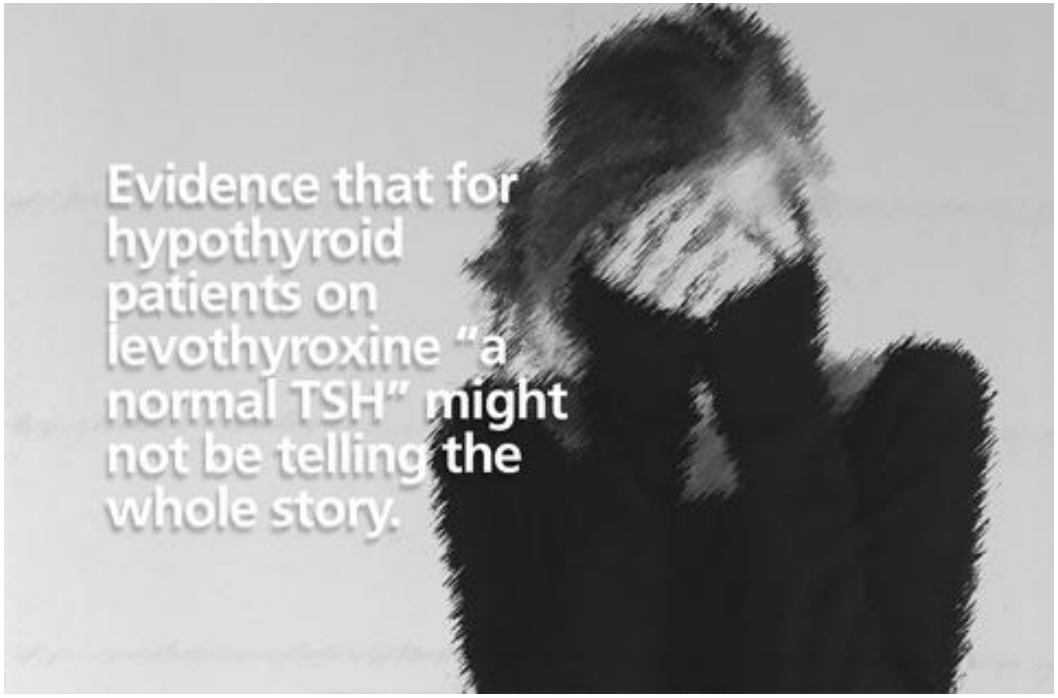
Mitsuru Ito, Akira Miyauchi, Shino Kang, Mako Hisakado, Waka Yoshioka, Akane Ide, Takumi Kudo, Eijun Nishihara, Minoru Kihara, Yasuhiro Ito, Kaoru Kobayashi, Akihiro Miya, Shuji Fukata, Hirotoshi Nakamura and **Nobuyuki Amino**

Eur. J Endocrinol, 2015

Patients groups N=253	TSH (mU/l)	FT_4 (pmol/l)	FT_3 (pmol/l)	FT_3/FT_4
Total thyroidectomy + L-T_4 ($n=103$)				
Pre-thyroidectomy	1.52 (1.02–2.13)	14.4 (13.3–15.4)	4.45 (4.06–4.81)	0.31 (0.28–0.34)
Post-thyroidectomy	0.78 (0.49–1.50)	17.2 (15.7–18.9)	4.29 (3.96–4.65)	0.25 (0.22–0.28)
P value	<0.001	<0.001	0.023	<0.001
Hemithyroidectomy + L-T_4 ($n=56$)				
Pre-thyroidectomy	1.84 (1.30–2.63)	13.8 (12.6–14.7)	4.38 (4.06–4.65)	0.32 (0.29–0.34)
Post-thyroidectomy	1.86 (1.16–2.75)	14.3 (13.2–15.4)	4.35 (3.98–4.61)	0.29 (0.27–0.33)
P value	0.136	0.024	0.498	0.017
Hemithyroidectomy alone ($n=94$)				
Pre-thyroidectomy	1.07 (0.73–1.51)	14.4 (13.1–15.3)	4.31 (3.89–4.77)	0.30 (0.27–0.33)
Post-thyroidectomy	2.41 (1.67–3.37)	12.9 (12.1–13.6)	4.43 (4.04–4.65)	0.34 (0.32–0.37)
P value	<0.001	<0.001	0.204	<0.001[a]

- Residual thyroid DIO2 activity essential for adequate peripheral T3 supply
- A case for less than total ThyreX when possible

Limitations to Retrospective Thyroidectomy Studies



- No insight into tissue levels
- No correlation with other parameters (RMR, QoL, lipids)
- Are the subjects with the lowest FT3/FT4 also the most symptomatic?

Is a Normal TSH Synonymous With "Euthyroidism" in Levothyroxine Monotherapy?

Peterson SA, McAninch EA, Bianco AC. *JCEM* 2016,101:4964–4973

- Cross-sectional study from publically available data
- 4 cycles NHANES (2001-12), full TFT's and normal TSH (0.24-5.2)
- 469 T4 users (no DTE or T3), 9152 healthy controls, 469 matched controls
- 52 laboratory and clinical parameters analyzed
- LT4 users had:
  - Higher T4, lower FT3, lower T3/T4 (15-20%)
  - Higher BMI but lower calorie intake
  - Lower METS
  - No major differences in QOL except for confusion
  - Greater use of anti-depressants, beta-blockers, statins

T3 Administration in the Treatment of Hypothyroid Patients?