Professor Ian Gilmore MD, PRCP.
President, the Royal College of Physicians,
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London, NW1 4LE

2nd April 2009

Dear Professor Gilmore,

Guideline on the Diagnosing and Management of Primary Hypothyroidism.

Although we appreciate the recommendation for investigating non-thyroid causes for the symptoms of hypothyroidism, the conclusions in the guideline destroy the diagnosis and management of the non-thyroid causes for the symptoms of hypothyroidism, which exist in those patients suffering deficiencies in peripheral metabolism and deficient peripheral cellular hormone reception (post thyroid deficiencies). The effect of this conclusion is simple – it will return many people to abject misery and will keep many more sufferers from ever realising their full potential.

When protocols of differential diagnosis, evidence based medicine, and hormone replacement are applied to the established medical science of post thyroid deficiencies, the result will be a rejection of the conclusions of this guideline, as they overreach into the non-thyroid gland realm of peripheral metabolism and peripheral cellular hormone reception.

In the 1960's, Refetoff noted that some patients were thyroxine resistant. In 1967, Refetoff et al. discovered peripheral cellular hormone reception. Three years later, Braverman, et al., completed the post thyroid picture with the discovery of peripheral metabolism. Numerous papers since have detailed their characteristics. They exist, as shown in the Thyroid Patient Advocacy-UK (TPA-UK) rebuttal to this guideline (enclosed). Since papers on medical science exist, they must be considered when establishing the diagnostic protocols. However, no guideline specifies a diagnostic procedure for these potential maladies. In fact, this guideline specifically ignores many of them. Furthermore, since the dominant hormone in the post thyroid realm is not thyroxine, but triiodothyronine, hormone replacement protocol demands replacement of triiodothyronine, not thyroxine.

Consequently, although this guideline appears reasonable, it is still debatable on the finer points, as long as it addresses primary hypothyroidism. However, as this guideline also impacts on post thyroid diagnosis and management, it is a detriment to the human rights of post thyroid deficient victims – who need T3.

Unfortunately, this battle has been confused by the lack of a proper definition of "hypothyroidism". We believe that if this definition were stipulated and logical consistency maintained, our viewpoints would begin to mesh.

Yours Sincerely,

Sheila Turner
Thyroid Patient Advocate
www.tpa-uk.org.uk
Cc to: Co-authors of the guideline on The Diagnosis and Management of Primary Hypothyroidism

Thyroid Patient Advocacy-UK Response to the Royal College of Physicians' Guideline on the Diagnosing and Management of Primary Hypothyroidism

"As often in the history of science, the biggest obstacle in finding the truth is not the difficulty in obtaining data, but the bias of the investigators on what data to chase and how to interpret them."

—Peter H. Duesberg, PhD, Inventing the AIDS Virus Washington, DC, Regnery Publishing, Inc., 1996

RCP Guideline or Diktat?

The Royal College of Physicians' (RCP) web site sets out their Clinical Guideline Standards. There is an urgent need for the RCP to indicate which Guideline Standard was used for the statements on the Diagnosis and Management of Primary Hypothyroidism. (1)

The release of the RCP's guideline, at first glance, appeared to offer hope with its admonitions for investigation of continuing symptoms, whether on thyroxine or not, for non-thyroidal causes of the symptoms. However, the guideline neither indicates the differential diagnostics for these continuing symptoms, nor does it suggest treatments - which leaves the question, will the old, patient abusing paradigm continue to prevail? Or, will medical science and ideals prevail?

The answer is most likely provided in the RCP's contradictory conclusion*:* All hopes for any rational standard for the treating of patients suffering with deficient peripheral metabolism or deficient peripheral hormone reception ('post thyroid' deficiencies) were dashed in conclusion (d). Here, the RCP returned to the pre-20th Century lack of appropriate therapy with their prohibition against any thyroid hormone therapy for continuing symptoms of hypothyroidism.

Unfortunately, because the basic science relating to patients suffering with post thyroid deficiencies is ignored, (2, 3) all other related interactions are ignored. At a minimum, the RCP guideline should acknowledge the possibility of this interaction.

The RCP et al. should retract the guideline and also retract the blanket proscription of prescribing triiodothyronine (T3) containing hormone replacements, desiccated thyroid in particular, since they are scientifically necessary for the well being of patients with deficient peripheral metabolism.

The RCP should, as its "Concise Guidance to Good Practice" requires, consider all the evidence available and make clear and logically consistent recommendations. Either post thyroid deficiencies should be disclaimed by a subsequent guideline, or they should be appropriately embraced.

The RCP statements violate the guideline authorship standards of care in "Concise Guidance to Good Practice" also written and promulgated by the Royal College of Physicians. This guideline adversely affects the health and well being of those patients who have the non-thyroid deficiencies in the peripheral metabolism of T4 to T3 or the hormone reception of T3 and it violates the protocols found in the "Concise Guidance to Good Practice" by the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians:

The Royal College of Physician's statements violate the guideline authorship standards of care in their "Concise Guidance to Good Practice" also written and promulgated by the Royal College of Physicians. The guideline on The Diagnosis and Management of Primary Hypothyroidism adversely affects the health and well being of those patients who have the non-thyroid deficiencies in the peripheral metabolism of T4 to T3 hormone, or the hormone reception of T3, and it violates the protocols found in the "Concise

Guidance to Good Practice" by the "Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians" as follows:

1. Guidelines should be discrete and can be considered in isolation -- but the diagnosis is not complete and the therapy is not adequate in all cases.
2. The conclusions do not improve quality of patient care and increases disability.
3. The lack of definitions in a vague realm does not clarify. However, the certainty that was produced by a wide variation of practices existed because there were a wide variation of causes - most of which were ignored.
4. The encouragement of objective methodology is misdirected as it only deals with thyroid gland deficiencies and not deficiencies that can exist between the thyroid gland and the symptom producing cells.
5. The literature search could not have been complete or it was selective as there are many, many articles on peripheral metabolism and peripheral cellular hormone reception.
6. There was no patient representation.
7. No references for the recommendations, particularly for the lack of therapy for those with "normal" hormone levels and continuing symptoms.
8. No evidence was offered, so it is not available to the reader - hence we cannot "decide on the reliability of the guideline." Further, by the logic in court cases dealing with enforced guidelines, they are not voluntary, but mandatory.
9. No stakeholder involvement statement.
10. No list of committee members (working party) or their areas of expertise.
11. No rigour in the development with respect to patients with deficient peripheral metabolism or deficient hormone reception.
12. No criteria for selecting evidence.
13. No evidence and consequently no explicit links.
14. No references.
15. The guideline conclusions do not correspond to the statement body of text.
16. It was not previewed by stakeholders
17. It does not meet the goals of the RCP - to serve patients well by setting high standards.
18. It does not champion the values or ethics of the medical profession with respect to the post thyroid deficient patient.
19. The health considerations were not made or addressed with regard to the post thyroid deficient patient. In fact for them, the guideline is quite depraved - ensuring them a life of misery.
20. There is evidence of potential funding issues and consequently the lack of independence.
21. With respect to the post thyroid deficient patient, the guideline makes diagnosis and treatment worse.
22. With respect of the post thyroid deficient patient, it is not patient centred and does not support ethical physicians.
23. With respect of the post thyroid deficient patient, it is a stain on the name of Royal College of Physicians.
24. Myth of Physician Independence

This situation demands a comparison between the objectives of the Royal College of Physicians, with the patients' experience.

> *Article 29 of the Magna Carta which is still enforced today.* "No Freeman shall be taken or imprisoned, or any other wise destroyed . . . but by lawful judgement of his Peers, or by the Law of the Land."

Patients suffering the symptoms and signs of hypothyroidism and its mimics are being destroyed without proper judgements.

Perhaps the earliest case occurred in England in the 17th Century. It was the Royal College of Physicians of London (established by King Henry VIII) versus Dr. Thomas Bonham, a Cambridge-educated physician. The Royal College did not appreciate non members practicing medicine in competition so they charged him with unlawful practice of medicine in spite of his vastly greater training than most practitioners of the healing arts of that day - including the fellows of the Royal College. After imprisonment by the Royal College, the Archbishop secured his release. Then Dr. Bonham and his attorney filed a suit against the Royal College for false imprisonment. Chief Justice of the Court of Common Pleas, Sir Edward Coke, found that the Royal College could not be a judge in matters in which it had a financial interest.

Coke believed that no man, even the king, is above the law. That should be today also.

Imprecise language prolongs suffering

A logical examination of a continuing medical education course(1) and the medical practice guidelines for hypothyroidism (2-9) finds that they are not clear.(10) They, like virtually all papers relating to hypothyroidism, do not stipulate a definition for "hypothyroidism." Although the two definitions for hypothyroidism were believed to be equivalent prior to 1967, subsequent medical science has definitively separated them.

The following two definitions are no longer equivalent:

The narrow, thyroid-centric definition is as the "-ism" suffix implies: "The clinical consequences of deficient secretion by the thyroid gland." This definition suggests potential deficiencies in the thyroid gland (primary hypothyroidism) or a preceding gland, the pituitary (secondary hypothyroidism) or the hypothalamus (tertiary hypothyroidism).

The broad, symptom-oriented definition, "The clinical consequences of inadequate levels of thyroid hormones in the body" (Taber's Cyclopaedia Medical Dictionary) suggests deficiencies in the hypothalamus-pituitary-thyroid axis ***plus*** the potential deficiencies in the peripheral metabolism and peripheral hormone reception, which are recognized by science, (11-18)

…which begs the question. If the "ism" in hypothyroidism is the deficient secretion by the thyroid gland, do the guidelines apply to post-thyroid effects on thyroid hormones?, or, if it is the deficient thyroid hormone levels, why isn't this stated in the guidelines to eliminate any risk of misinterpretation and why do the guidelines recommend diagnostics and therapies that only apply to the thyroid gland? Why don't the guidelines contain ANY diagnostics and therapies for any post-thyroid operation, which have been known to medical science for the past 40 years?

The usual hypothyroidism guideline draws patients into its protocol by the existence of symptoms, i.e., the broad definition of hypothyroidism. However, these guidelines then diagnose and treat these patients according to the narrow, thyroid-centric definition. (1,2-9) For hypothyroidism, the only indicators assayed and considered are the following:

1. Thyroid Stimulating Hormone (TSH or Thyrotropin) – the "input" to the thyroid.
2. Free Thyroxine) FT4 – the primary "output" of the thyroid.
3. Thyroid antibodies – an indicator of internal thyroid problems.

The dominant post-thyroid hormone, triiodothyronine (T3), is not assayed. Additionally, an indicator of post-thyroid deficiencies, reverse triiodothyronine (rT3) is not assayed such as suggested by Brady in

Table 2 of *Functional Thyroid Disorders.*(19) Neither is the T3 level in a 24-hour urine sample as suggested by Baisier, et al.(20) Further, the clinical diagnostic algorithm upon a combination of symptoms by Baisier, et al.,(20) is completely ignored – probably because individually the symptoms are "non-specific."

A guide for the authorship and "repair" of the medical practice guidelines has been written.(21) Table 4 of this protocol for authoring medical practice guidelines(21) demands the stipulation of definitions of words and terms that are "unfamiliar, critical, or subject to misinterpretation." In other words, the medical practice guidelines for hypothyroidism should have stipulated the definition for "hypothyroidism" because it is both subject to misinterpretation and critical to the guideline even though they use "thyroid" in their title.(3,9,22) Of course, common sense suggests making important matters clear.

Patients with exo-endocrine (or post thyroid) deficiencies would be diagnosed and treated properly if the definition of "hypothyroidism" were stipulated and logical consistency maintained in one of two ways.(10)(17) If the broad, symptom-oriented definition where stipulated, then the medical practice guideline would need expansion to include the additional diagnostic and treatment protocols. If the narrow, thyroid-centric definition were stipulated, then the medical practice guideline would not be applicable to post-thyroid or exo-endocrine deficiencies.

The patient-physician relationship would then be changed from win-lose to win-win by stipulating either definition.(10) If the broad definition were stipulated and logical consistency maintained, the physician would be guided towards the proper therapy, the patient would recover his/her well-being and the physician would not suffer any liability to the GMC. If the narrow definition were stipulated, then the exo-endocrine deficiencies would not be in the guideline's jurisdiction. The physician, since there is no guideline for post thyroid etiologies, could use his best judgment without undue liability to the GMC.(10)

However, the choice has already been made. Patient information for hypothyroidism already stipulates the narrow, thyroid-centric definition: "Hypothyroidism (underactivity of the thyroid gland) occurs when the thyroid gland produces less than the normal amount of thyroid hormone".(23)

Unfortunately, the UK patient information (24) uses the broad definition. This reinforces the confusion noted by Toft and Beckett, see quote above. (25) More unfortunately, because the basic science of post-thyroid operations are ignored(26,27) all interactions between the post-thyroid realm and the thyroid are also ignored. At a minimum, the guidelines should acknowledge the possibility of this interaction.

References:

1. *Gossel, TA, Endocrinology Continuing Education accredited by the Accreditation Council for Continuing Medical Education (ACCME), 2005*
2. *Baskin, HJ, MD, Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism, Am Assoc Clin Endocrinol, 2002, Rev 2006*
3. *Levy EG, Ridgway EC, Wartofsky L, Algorithms for Diagnosis and Management of Thyroid Disorders, www.thyroidtoday.com 2004.*
4. *The American Thyroid Association provides links to several hypothyroidism related guidelines: "Use of Laboratory Tests in Thyroid Disorders," "Treatment Guidelines for Patients with Hyperthyroidism and Hypothyroidism," and "Guidelines for Detection of Thyroid Dysfunction."*
5. *Levy EG, Hypothyroidism Treatment Failure: Differential Diagnosis, www.thyroidtoday.com 2004.*
6. *Vanderpump MPJ, Ahlquist JAO, Franklyn JA, et al., Consensus Statement for Good Practice and Audit Measures in the Management of Hypothyroidism and Hyperthyroidism, BMJ, August 1996*
7. *Garber JR, Hennessey JV, Lieberman JA, Morris CM, Talbert RI, Managing the Challenges of Hypothyroidism, Supplement to J of Fam Pract, 2006, www.jponline.com*
8. *Kaplan MM, Clinical Perspectives in the Diagnosis of Thyroid Disease, Clin Chem, 1999, 45:8(B) 1377-1383*
9. *UK Guidelines for the Use of Thyroid Function Tests, The Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation, 2006, www.british-thyroid-association.org/guidelines.htm*

10. *Pritchard EK, "The Linguistic Etiologies of Thyroxine-Resistant Hypothyroidism," Thyroid Science www.thyroidscience.com – click on "debate."*
11. *Visser TJ, Leonard JL, Kaplan MM, Larsen PR, Kinetic Evidence Suggesting Two Mechanisms for Iodothyronine5'-deiodination in Rat Cerebral Cortex, Proc. Natl Acad Sci. USA, August 1982, 79:5080-84*
12. *Kaplan MM, Utiger, RD, Iodothyronine Metabolism in Rat Liver Homogenates, J Clin Invest, February 1978, 61:459-471*
13. *Hidal JT, Kaplan MM, Characteristics of Thyroxine 5'-Deiodination in Cultured Human Placental Cells Regulation by Iodothyronines, September 1985, J Clin Invest, 76:947-955*
14. *Kaplan MM, Yaskoski KA, Maturational Patterns of Iodothyronine Phenolic and Tyrosyl Ring Deiodinase Activities in Rat Cerebrum, Cerebellum, and Hypothalamus, J Clin Invest, April 1981, 67:1208-1214*
15. *Braverman LE, Ingbar SH, Keinwem S, Conversion of Thyroxine (T_4) to Triiodothyronine (T_3) in Athyreotic Human Subjects, The J Clin Invest, 1970, 49*
16. *Danzi S, Ojamaa K, and Klein I, Triiodothyronine-Mediated Myosin Heavy Chain Gene Transcription in the Heart, Am J Phys Heart Circ Physiol, Feb 27, 2003*
17. *Eisenstein Z, Hagg S, Braverman LE, et al., Effect of Starvation on the Production and Peripheral Metabolism of 3,3',5' Triiodothyronine in Euthyroid Obese Subjects, J Clin Endocrinol Metab, 1978, 47(4): 889-893*
18. *Nomura S., et al. Reduced Peripheral Conversion of Thyroxine to Triiodothyronine in Patients with Hepatic Cirrhosis, J of Clin Invest, Sept 1975, 56(3): 643-652.*
19. *Brady, D, Functional Thyroid Disorders, Part I, Dynamic Chiropractic, March 20, 2000, 18(7), Table 2*
20. *Baisier, WV, Hertoghe, J., Beekhaut, W., Thyroid Insufficiency? Is Thyroxine the Only Valuable Drug?, J Nutr and Environ Med, September 2001, 11(3):159-166*
21. *Mechanic JI, Berman DA, Braithwaite SS, Palumbo PJ, American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Practice Guidelines, Endocr Pract, 2004, 10(4), Table 4*
22. *Kaplan MM, Clinical Perspectives in the Diagnosis of Thyroid Disease, Clin Chem, 1999, 45:8(B) 1377-1383*
23. *Hypothyroidism, a publication by the American Association of Clinical Endocrinologists and supported by Abbott Laboratories. 2006 & 2008. www.thyroidawareness.com*
24. *Hypothyroidism – Clinical Features and Treatment, a publication of the British Thyroid Association, www.british-thyroid-association.org/guidelines.htm*
25. *Toft A, Beckett G, BMJ 2003 (8 Feb); 326:295-296*
26. *Gossel, TA, Endocrinology Continuing Education accredited by the Accreditation Council for Continuing Medical Education (ACCME), 2005*
27. *Garber JR, Hypothyroidism—Talking Points 2006, AACE*

Medical Practice defined by Mandatory Guidelines?

Guidelines are not advisory when there is guideline enforcement in the picture. They are mandatory, in spite of the disclaiming statement on the BTA, ACB, BTF UK Guidelines on Thyroid Function Tests(1) and the disclaiming statement in the RCP Clinical Guideline Standards.(2)

> *BTA: "The document should be considered as guidelines only; it is not intended to serve as a standard of medical care. The doctors concerned must make the management plan for an individual patient. The focus of the document is thyroid function testing, and it is not intended to be a comprehensive text on thyroid disorders.*
>
> *RCP: "For those not familiar with guidelines, we would point out that the recommendations from guidelines are expected to apply to the majority of patients with a particular condition. They are not protocols of care and there will be and should be exceptions that require individualised care outside the guideline recommendations."*

Doctors have been prosecuted for not adhering to "voluntary" and incomplete guidelines.

The US Supreme Court in *Goldfarb v. Virginia State Bar*, 421 U.S. 773, (1975), found that guidelines that were accompanied by potential disciplinary action were not voluntary, despite the defendants' insistence. Such guidelines are mandatory. If guidelines were not enforced, they would truly be voluntary. However, the General Medical Council enforces medical practice guidelines, often at the instigation of the accused. Such enforcement makes these guidelines mandatory. While this should be quite obvious, and probably

can be found in the law of the United Kingdom, it is found in American case law. Consequently, in spite of the disclaiming statement in the BTA, BTF, ACB UK guideline,(1) it IS mandatory.

The law is not fond of unresolved issues and will follow the generally accepted interpretation. The present case is the boycotting of all alternatives to levothyroxine sodium. The physician who dares defy the medical guidelines for the benefit of the patient can find him/herself in substantial and costly disciplinary difficulties with the GMC, even if the doctor is treating his patient ethically and scientifically.

The BTA has formulated and foisted a sham consultation process onto the RCP, and it must be exposed for its duplicity. It has ignored swathes of patients who have repeatedly been unable to prosper on just levothyroxine; personal experience indicates that this RCP protocol is misguided in the extreme and that it will continue to cause inadvertent deaths in unsuspecting patients, improperly advised as to the alternative therapies.

The RCP has failed to consult those patients in diametric opposition to their guideline in the UK. Thyroid Patient Advocacy-UK (www.tpa-uk.org.uk), Thyroid-UK (www.thyroiduk.org) and Thyroid Disease (www.thyroid-disease.org.uk) to mention just three, who represent tens of thousands of UK patients. They have not been approached for their views. The RCP has, in fact, tried to discredit and denigrate those very people who oppose them, first, by silence, then by riding roughshod over their desperate need for a cure, and to use their 'collective' power to terrorise doctors into submission, even when these doctors know that the suggested protocol is wrong.

The ‘guideline’ does not meet the goals of the RCP - to serve patients well by setting high standards, neither do they champion the values or ethics of the medical profession with respect to the ‘post thyroid’ deficient patient. With respect of these patients, it makes diagnosis and treatment worse, it is not patient centred and does not support ethical physicians. With respect of the ‘post thyroid’ patient, it is a stain on the name of the Royal College of Physicians.

We can only hope that some court will order this guideline to be revised in the same manner that the Infectious Disease Society of America is now doing in an agreement with the Attorney General of Connecticut.(3)

1. no past guideline author may participate,
2. all, not selected, medical science must be considered,
3. the committee meetings must be open to the public, and
4. the committee must have an ombudsman that is mutually chosen.

If this were done in respect of hypothyroidism and its mimics, then patients unable to make T3, or with peripheral cell receptor problems, would not continue to suffer.

A Degree of Autonomy for Medical Practitioners

The RCP has created a “guideline” that has not put the interest of patients foremost and taken away the right for medical practitioners to exercise their professional clinical judgement.(4) According to the Medicines and Healthcare Regulatory Agency (MHRA) Review of Unlicensed Medicines, they make the point that:

> *“Clinicians should have the ability in appropriate circumstances to exercise their professional judgement to commission the supply of an unlicensed medicine to meet the special needs of an individual patient”.*(5)

Campaign of Denigration

It does appear that a campaign of denigration has been organised by a cabal of interested parties in trying to maintain their 'position of trust' in the face of a stark and intransigent opposition to a malign policy being foisted upon an increasingly disaffected body of patients who remain resolutely ill.

In a survey of 1500 hypothyroid patients undertaken by Thyroid Patient Advocacy-UK (TPA-UK) in 2005-2006,(6) the dissatisfaction of many patients is highlighted. This survey has very good credentials that it points to inconsistencies within the data presented by the BTA as being 'definitive'. Why has the RCP and BTA et al., chosen to take no account of these statistics when a copy was sent to Professor Anthony Weetman in 2006 (then President of the BTA) and every member of the BTA Executive Committee. No response or acknowledgement has ever been received from them. This hypothyroid survey should be held up as valid, contradictory evidence to the RCP guideline.

Of 1500 respondents to this survey, 93.8% (n=1407) had not been told of medicines other than L-thyroxine by their medical practitioner. 38.8% (n=768) felt they had "not been dealt with very well" or "not very well at all" by their doctor whilst seeking a diagnosis of their symptoms; 233 (15.5%) had given up paid employment; 300 (20%) had taken time off work as a result of thyroid illness; 500 (33.3%) felt their close relationships had been affected by thyroid illness and 632 (42.1%) had stopped or altered their exercise routines as a result of their symptoms. When asked of those patients undergoing L-thyroxine therapy, "Do you feel that you have fully regained your optimal state of health?" **1176 (78.4%) Answered "NO**". What did the BTA say in reply – **NOTHING!**

Evidence-Based Medicine – Relevance or Repudiation?

Although 'evidence based medicine' is to be applauded, much of the evidence base for the treatment of hypothyroidism is based on research that does not consider the patient's experience and may be flawed.(7-9)

The paper "Evidence Based Medicine Leads to Mediation of Symptoms of Mimics of Hypothyroidism"(10) should be compulsory reading for every medical practitioner.

1. Science has discovered the sources of these mimics of hypothyroidism.
2. Evidence Based Medicine and Differential Diagnosis protocols demand that these mimics be considered.
3. The endocrinology establishment does not recognise them, does not recommend any diagnostics for them, and bans the mitigating and managing therapy for them.

Evidence Based Medicine (EBM) is a modern, scientific alternative to the Eminence Based Medicine. Currently, eminence based medicine continues to ignore all mimics of hypothyroidism as do the RCP guidelines on the diagnosis and management of hypothyroidism. Evidence Based Medicine(11,12) is the conscious, explicit, and judicious use of best evidence in making decisions about the healthcare of patients. EBM is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions. EBM can, if given a chance, produce a solution to quite unsatisfactory results of extensive hypothyroidism diagnostics and therapy attempts. It can, because there ARE physical reasons for the continuing symptoms. The information about these causes and treatments of these symptoms exists.

The clinical practices upon the mimics of hypothyroidism have exemplified the following point:

"For decades people have been aware of the gaps between research evidence and clinical practice, and the consequences in terms of expensive, ineffective, or even harmful decision making."*(9)*

Indeed, the clinical practice upon these mimics has been limited to declaring them “functional somatoform disorders”(13,14) and their symptoms “non-specific.”(15,16) These diagnoses have several problems. They are suspect, since millions,(17,18) are not likely to be delusional. These diagnostics are illogical,(19) and pending the investigation “on the state of medical science”,(20) are also incorrect.

TPA-UK believes that the RCP guideline does not consider the patient’s experience and that it fails to present a balanced argument based on the available evidence.

Is it any wonder that Doctors Anthony Toft and Geoffrey Beckett were puzzled,(21)

> *“It is extraordinary that more than 100 years since the first description of the treatment of hypothyroidism and the current availability of refined diagnostic tests, debate is continuing about its diagnosis and management.*

TPA-UK therefore provides herewith a rebuttal to this guideline based on the literature and available research evidence not considered by the RCP et al.

References:

1. *British Thyroid Association, British Thyroid Foundation, Association of Clinical Biochemists (2006)UK Guidelines on Thyroid Function Tests , www.british-thyroid-association.org/guidelines.htm*
2. *Royal College of Physicians (London) “What are Clinical Guidelines?” http://www.rcplondon.ac.uk/college/ceeu/search/)*
3. *IDSA Agreement with the Connecticut Attorney General http://www.lyme.org/updates.html*
4. *The Royal College of Physicians “Patients need UK medicines strategy” Press Release. http://www.politics.co.uk/opinion-formers/press-releases/health/patients-need-uk-medicines-strategy-says-rcp-$1266188$365674.htm*
5. *Medicines and Healthcare Products Regulatory Agency. Review of unlicensed medicines. http://www.mhra.gov.uk/Howweregulate/Medicines/Reviewofunlicensedmedicines/index.htm}*
6. *Turner S, Hypothyroidism Patient Survey Results, Thyroid Patient Advocacy-UK, http://www.tpa-uk.org/tpauk_hypothyroidsurvey.php*
7. *Carr, C., McLeod, D.T., Parry, G., et al. “Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment.” Clin. Endocrinol., 28:325-333, 1988.*
8. *Schlote, B., Schaaf, L., Schmidt, R., et al. “Mental and physical state in subclinical hyperthyroidism: investigation in a normal working population.” Biol. Psychiatry, 32(1):48-56, 1992.*
9. *Schlote, B., Nowotny, B., Schaaf, L., et al. “Subclinical hyperthyroidism: physical and mentalstate of patients.” Eur. Arch. Psychiatry Clin. Neurosci., 241(6):357-364, 1992.*
10. *Pritchard E.K ”Evidence Based Medicine Leads to Mediation of symptoms of Mimics of Hypothyroidism”. Thyroid Patient Advocacy-UK http://www.tpa-uk.org.uk/pritchard3_ebm.pdf*
11. *Rosenberg W, Donald A, Evidence based medicine: an approach to clinical problem-solving, BMJ1995;310:1122-1126 (29 April*
12. *Sackett DL, Rosenberg MC, Muir Gray JA, Haynes RB, Richard WS, Evidence Base Medicine: What It Is and What It Isn’t, BMJ, 1996; 312:71-7*
13. *Weetman AP, Who’s Thyroid Hormone Replacement is it Anyway? Clin Endocrinol, 2006;64(3):231-23*
14. *Salmon P, Peters S, Stanley I, Patients’ Perceptions of Medical Explanations for Somatisation Disorders: Qualitative Analysis, BMJ, 1999; 318:372-37*
15. *“Wilson’s Syndrome,” American Thyroid Association, Nov 1999 updated May 200*
16. *Barsky, AJ, MD and Borus, JF. MD, Functional Somatic Syndromes, Ann Intern Med, June 1999, 130(11):910-921*
17. *Saravanan P, Chau F, Roberts N, Vedhara K, Greenwood R, Dayan CM, 2002, Psychological Well-Being in Patients on “Adequate” Doses of L-Thyroxine Results of a Large, Controlled Community-Based Questionnaire Study, Clinical Endocrinology, 2002, 57: 577-58*
18. *Patients’ Petition for Better Diagnosis and Treatment Choice for Hypothyroid Patients, International Hormone Society, http://inthormonesociety.org*
19. *Pritchard EK, “The Linguistic Etiologies of Thyroxine-Resistant Hypothyroidism,” Thyroid Science www.thyroidscience.com – click on “debate.*
20. *Sharpe M, Carson A, “Unexplained Somatic Symptoms, Functional Syndromes, and Somatization: Do We Need a Paradigm Shift?, Ann Intern Med, 2001, 134:926-93*
21. *Toft A, Beckett G, BMJ 2003 (8 Feb); 326:295-296*

Inadequacy of Serum Thyroid Function Testing

If the RCP believe biochemical testing is the gold-standard, then they would be doing a service to thyroid patients and the endocrinology speciality in calling for a complete re-evaluation of the reference ranges for normal TSH levels, so that the numbers they wish to rely so heavily on are in fact valid. The RCP should be advocating the inclusion of antibodies testing as part of any standard thyroid panel to uncover thyroid disease and hypothyroidism. While the RCP offer their opinions in this guideline, it is important to remember that they are just that –opinions.

Opinions should not guide the diagnosis and treatment of primary hypothyroidism. Because ultimately, the validity of research on the way hypothyroidism is diagnosed and treated rests on an outdated TSH reference range that screams out for a complete re-evaluation and revamping. A re-evaluation of the TSH reference range must be the first priority among many much-needed and essential reforms to conventional thyroid doctrine and practice.

The diagnosis and treatment of hypothyroidism should be straight forward: a few blood tests and visits to a GP, after which many should be helped to regain their normal health. However, other patients and their doctors find it a mystery that is inappropriately excused with “nonspecific symptoms” or “functional somatoform disorders.” Amazingly, the symptoms that prompted the assays in the first place are not regarded as sufficient for further investigation - but the mimics of hypothyroidism require consideration too and must not be ignored. Ignoring medical science has produced a 13% failure rate amongst those treated for hypothyroidism as indicated in one study,(1) and yet more, in another.(2) A patient petition demanding better diagnosis and treatment has been signed by over 1300 patients so far.(3) Without a doubt, there is a distinct need. A physician consensus petition, with 2000 signatories, demands the right to prescribe the physiologically required therapy.(4)

Medical practice guidelines should describe applicable physiology, the symptoms of the etiologies, the applicable differential diagnostics, and the therapy approaches as dictated by the diagnostic results. Unfortunately, medical guidelines do not live up to their purpose. Studies of medical guidelines (5-7) give the average guideline a seriously failing grade. Very few are excellent.

References:

1. *Saravanan P, Chau F, Roberts N, Vedhara K, Greenwood R, Dayan CM, 2002, Psychological Well-Being in Patients on “Adequate” Doses of L-Thyroxine Results of a Large, Controlled Community-Based Questionnaire Study, Clinical Endocrinology, 2002, 57: 577-585*
2. *Turner S, Hypothyroidism Patient Survey Results, Thyroid Patient Advocacy-UK, http://www.tpa-uk.org.uk/tpauk_hypothyroidsurvey.php*
3. *Patients’ Petition for Better Diagnosis and Treatment Choice for Hypothyroid Patients, International Hormone Society http://www.intlhormonesociety.org/index.php?option=com_content&task=view&id=31&Itemid=53&tomHack_idp=10*
4. *Physician Consensus, International Hormone Society, http://intlhormonesociety.org/index.php?option=com_content&task=view&id=37&Itemid=71*
5. *Shaneyfelt TM, Mayo-Smith MF, Rothwangl, J, Are Guidelines Following Guidelines?, JAMA, May 26, 1999., 281(20)*
6. *Grilli R, Magrini N, Penna A, Mura G, Liberati A, Practice Guidelines Developed by Specialty Societies: The Need For a Critical Appraisal, Lancet, Jan 8, 2000.*
7. *Burgers JS, Fervers B, Haugh M, Brouwers M, Browman G, Cluzeau PFA, Internatinal Assessment of the Quality of Clinical Practice Guidelines in Oncology Using the Appraisal of Guidelines and Research and Evaluation Instrument, J Clin Oncol, May 15, 2004, 22(10)*

Dismissal of all other assays?

There is a large body of evidence to support the use of 24 hour urine testing for thyroid dysfunction. Excellent papers are available to point out their efficacy but have been ignored.(1) Analytical and clinical validation has been shown to anyone who will read it, or listen. The 24 hour urine thyroid function test is generally to be preferred over standard serum TFT because it shows the amount of thyroid **being used**, not simply how much is there – and perhaps **not** being used (2-21).

In this world of EBM, this has come to mean that the evidence is narrowed down to clinical assays only. It should go without dispute that the physicians' observations should not only be included in this evidence, but, indeed, have precedence over the tests. In this connection the Barnes Basal temperature test does not deserve the implied opprobrium heaped on it by RCP. It is a most valuable tool as a screening test, and the RCP misunderstands its role when they suggest it is being used to make the diagnosis. In fact a low basal temperature points the way to a fuller clinical appraisal, and it is here that it's great value lies.

However, there is much evidence to support the measurement of basal body temperature in the diagnosis of thyroid dysfunction. Dr. Broda Barnes discovered in the course of performing basal metabolism tests that patients suffering the symptoms and signs of hypothyroidism also suffered from low body temperatures.(22) Upon further investigation, he learned that this simple test was an excellent, although not a totally accurate indicator of hypothyroidism. This test is also used by others(23,24) but is also disparaged(25) by citing a study on body temperatures.(26) Like the somatic studies below, this study did not screen patients with physical complaints that might lower their body temperature, including hypothyroidism. Thus, the logical error of attempting to distance the symptom from hypothyroidism, again used data tainted by hypothyroidism.(27)

Sufficiently low body temperatures are described as hypothermic. Although general concerns by physicians only starts below 95 degrees Fahrenheit, the differential diagnosis for hypothermia is revealing.(28) In addition to exposure, which is well down the list, it places a variety of hormone deficiencies at the top of the list, with hypothyroidism, and presumably its mimics, first. Thus, Dr. Barnes is substantially, although not always, correct – a fact which he noted as well.

The stark contrast between Dr. Broda Barnes' use of the low basal temperature indicator, and its rejection,(25) coupled with the comparison of the inclusive differential diagnostics for hypothermia,(28) with the exclusive differential diagnostics for hypothyroidism,(29-36) in particular, those in the UK guidelines,(37-40) suggests that instead of caring for the patient,(28) the important role is selling levothyroxine sodium to the exclusion of other hormone replacements, which are potentially needed hormone replacements.(37-40)

References:

1. *Fraser WD, Biggart E, O'Reilly D St J, Gray H W, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J. 1986, 293: 808-10*
2. *Chan V, Landon J. Urinary thyroxine excretion as index of thyroid function. Lancet. 1972, (Jan 1) 7740: 4-6*
3. *Tal E , Sulman FG. Urinary thyroxine. Lancet. 1972, 1291*
4. *Chan V, Besser GM, Landon J, Ekins RP. Urinary triiodothyronine excretion as index of thyroid function. Lancet 1972, (Aug 5) 253-256*
5. *Chan V, Besser GM, Landon J. Effects of oestrogen on urinary thyroxine excretion. Br Med J. 1972, 4: 699-701*
6. *Rastogi GK, Sawhney, Sinha, Thomas, Devi. Serum and urinary levels of thyroid hormones in normal pregnancy. Obstet Gynecol. 1974, 2: 176-80*
7. *Rogowski P,Siersbaek-Nielsen K, Mölholm Hansen J. Urinary excretion of thyroxine in different thyroid states. Acta Endocrinol (Kopenh). 1978, 87: 525-3*
8. *Kolendorf K, Broch Môller B, Rogowski P. The influence of chronic renal failure on serum and urinary thyroid hormone levels. Acta Endocrinol (Kopenh). 1978, 89: 80-8*
9. *Ali Afrasiaki M, Dabir Vaziri N, Grant Gwinup, Mays M, Barton CH, Ness RL,Valenta LJ. Thyroid function in the nephrotic syndrome. Ann Int Med. 1979, 90, 335-8*
10. *Aizawa T, Yamada T, Tawata M, Shimizu T, Furuta S, Kiyosawa K, Yakata M. Thyroid hormone metabolism in patients with liver cirrhosis, as judged by urnary excretion of triiodothyronine. J Am Geriatrics Soc. 1980;28(11):485-91*
11. *Yoshida K, Sakurada T, Kaise K, Saito S, Yoshinaga K. Measurement of triiodothyronine in urine. Tohoku J Exp Med. 1980;132(4):389-95*
12. *Lopresti JS, Warren DW, Kaptein EM, Croxson MS, Nicoloff JT. Urinary immunoprecipitation method for estimation of thyroxine to triiodothyronine conversion in altered thyroid states. J Clin Endocrinol Metab. 1982;55(4):666-70*
13. *Yoshida K, Sakurada T, Kaise K, Yamamoto M, Saito S, Yoshinaga K. Thyroid stimulation test with urinary T3 concentration as an index of thyroid response. Tohuku J Exp Med. 1983;139(3):271-7*
14. *Mirralles-Garcia JM, Mories-Alvarez MT, Reglero-Chillon A, Lanao JM, Corrales-Hernandez JJ, Garcia-Diez LC. Urinary kinetics of triiodothyronine and their modification with age. Horm Metab Res. 1985;17(7):366-9*

15. *Orden I, Pie, Juste, Marsella, Blasco. Thyroxine in unextracted urine. Acta Endocrinol (Kopenh). 1987;114:503-8*
16. *Faber J, Siersbaek-Nielsen K, Kirkegaard C. Renal handling of thyroxine, 3,5,3'- and 3,3',5'-triiodothyronine, 3,3'-diiodothyronine in man. Acta Endocrinol (Kopenh). 1987;115:144-8*
17. *Orden I, Pie J, Juste MG, Giner A, Gomez ME, Escanero JF. Urinary triiodothyronine excretion. Rev Espan Fisiol. 1988;44 (2):179-84*
18. *Hertoghe J. The usefulness of evaluating the urinary excretion of triiodothyronine and thyroxine in the urines of 24 hours for diagnosis of thyroid dysfunction and follow-up of thyroid treatment. Conference in Antwerp, Belgium, March 1975*
19. *Baisier WV, Hertoghe J, Eeckhaut W. Thyroid insufficiency. Is TSH the only diagnostic tool? J Nutr Env Med. 2000; 10: 105-13*
20. *Baisier WV, Hertoghe J, Eeckhaut W. Thyroid insufficiency. Is thyroxine the only valuale drug? J Nutr Env Med. 2001;11:159-166*
21. *Hertoghe T. The efficacy of diagnosing borderline and overt hypothyroidism with the laboratory assessment of triiodothyronine and thyroxine excretion in the urines of 24 hours. A comparison with plasma thyroid tests. Optimal hormone therapy in the aging adult. Basic and advanced seminar, San Francisco, February, 2000*
22. *Barnes, B MD, Hypothyroidism: The Unsuspected Illness, Harper & Row, 1976*
23. *Starr, Mark MD, Hypothyroidism Type 2, Mark Starr Trust, Columbia, MO, 2005*
24. *Lowe JC, The Metabolic Treatment of Fibromyalgia, McDowell Publishing Company, 2000*
25. *"Wilson's Syndrome," American Thyroid Association, Nov 1999 updated May 2005*
26. *Mackowiak, et al., A Critical Appraisal of 98.6 Degrees F, the Upper Limit of the Normal Body Temperature, and other Legacies of Carl Reinhold August Wunderlich, JAMA, 1992, 268:1578-80*
27. *Pritchard EK, "The Linguistic Etiologies of Thyroxine-Resistant Hypothyroidism," Thyroid Science www.thyroidscience.com – click on "debate."*
28. *Differential Diagnosis of Hypothermia, http://pier.acponline.org/physicians/public/d598/tables/d598-tddx.html*
29. *Baskin HJ, MD, Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism, Am Assoc Clin Endocrinol, 2002, Rev 2006*
30. *Levy EG, Ridgway EC, Wartofsky L, Algorithms for Diagnosis and Management of Thyroid Disorders, www.thyroidtoday.com 2004.*
31. *The American Thyroid Association provides links to several hypothyroidism related guidelines: "Use of Laboratory Tests in Thyroid Disorders," "Treatment Guidelines for Patients with Hyperthyroidism and Hypothyroidism," and "Guidelines for Detection of Thyroid Dysfunction."*
32. *Levy EG, Hypothyroidism Treatment Failure: Differential Diagnosis, www.thyroidtoday.com 2004.*
33. *Vanderpump MPJ, Ahlquist JAO, Franklyn JA, et al., Consensus Statement for Good Practice and Audit Measures in the Management of Hypothyroidism and Hyperthyroidism, BMJ, August 1996*
34. *Garber JR, Hennessey JV, Lieberman JA, Morris CM, Talbert RI, Managing the Challenges of Hypothyroidism, Supplement to J of Fam Pract, 2006, www.jponline.com*
35. *Kaplan MM, Clinical Perspectives in the Diagnosis of Thyroid Disease, Clin Chem, 1999, 45:8(B) 1377-1383*
36. *UK Guidelines for the Use of Thyroid Function Tests, The Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation, 2006, www.british-thyroid-association.org/guidelines.htm*
37. *Baisier, WV, Hertoghe, J., Beekhaut, W., Thyroid Insufficiency? Is Thyroxine the Only Valuable Drug?, J Nutr and Environ Med, September 2001, 11(3):159-166*
38. *Gaby AR, Sub-Laboratory Hypothyroidism and the Empirical use of Armour® Thyroid, Alt Med Rev, 2004, 9(2)*
39. *Danzi S and Klein I, Potential Uses of T_3 in the Treatment of Human Disease, Clin Cornerstone, 2005, 7(S2): S9-S15*
40. *Hertoghe T, Nabet JJ, The Hormone Solution, Harmony Books, 2002*

Further obfuscation on validity of blood tests.

> *The RCP state the results of blood tests can be influenced by other factors e.g. in some illnesses which do not affect the thyroid gland, in which case, the tests will normalise after the illness has retreated.*

This is a desperately meaningless and unhelpful obfuscation of the issues. Such "other factors" will be obvious to the clinician, who will base any intervention on need at the time. The all present threat that treatment can be harmful assumes the physician is unaware of the factors, and potential harm, which is quite insulting; or that he/she will be unaware of the evolution of the "other illness". The hollowness and absurdity of the author's writing is well evident in this statement.

Thyroid function blood test results can be influenced by many factors, any of which should be taken into consideration, e.g.

- Labelling errors
- Bacterial contamination

- Yeast/Fungal contamination
- Clotting
- Sampling errors
- Sample preparation errors
- Sample storage errors
- Thermal cycling
- Antithyroid antibodies (any)
- Antibodies from any other cause
- Presence of specific ‘toxins’ in the blood
- Presence of pharmaceutical drugs (interferences) within the blood
- The method of analysis being carried out eg radio-immune assay (RIA)
- ‘Systematic’ errors in analytical equipment or methodology
- Composite errors <> pre-analysis (not mentioned above)
- MCT8 mutations

It is also known that thyroid function tests will be normal in almost every case if patients previously had X-ray therapy as a child for enlarged adenoids or tonsils, enlargements of the thymus gland as a newborn, birthmarks, whooping cough, acne, or ringworm of the scalp. Thyroid function tests will be normal also in patients who have a proven carcinoma. The T4 and TSH value can be misleading in such cases.

Many individuals with classic symptoms of hypothyroidism, such as low body temperature, joint pain, fatigue and depression, are discouraged when they’re told that their thyroid hormone levels are within the normal range. The question of whether they might be resistant to their body’s own thyroid hormone is seldom considered. Yet, a disease known as thyroid hormone resistance can prevent thyroid hormone from reaching the body’s cells.

The discovery of MCT8 mutations explains laboratory discrepancies (1) e.g. cases in which the lab results didn’t fit a particular pattern. It also explains how thyroid hormone resistance can cause TSH to appear normal even with a low FT4. In many instances only the TSH test is performed. If the TSH result is normal, and symptoms of hypothyroidism are observed, tests for FT4, FT3 and T3 should all be performed.

None of these types of error are ever shown as being part of the reference range, but they all add to the unquantifiable ‘unreliability’ of the final number that appears on a lab report; stated to be within/outside a reference range. The labs expect, but often don’t get, notification of antibodies found by other labs or by investigations showing antibody activity, to enable proper screening (dilutions) for likely errors. e.g. vitiligo, alopecia, ongoing autoimmune symptoms specific to such as lupus, autoimmune attacks on specific organs, histology samples, haematological examinations.(2) A search on Pubmed shows 126 such cases.

That Fickle TSH?

> *The RCP state that fine-tuning of TSH levels inside the reference range may be needed for individual patients and that, patients with continuing symptoms after appropriate Thyroxine treatment, should be further investigated to diagnose and treat the cause.*

This is the same as saying that any one within the reference range can be suffering from hypothyroidism. Since we are dealing with human beings, there will need to be ‘fine tuning’ for <u>all</u> patients. And is it so unreasonable to judge the dosage and fine tuning by the patient response? Patients could be asked how they feel; their pulse rate and temperature could be used instead of, or alongside if need be, interminable and frequently inaccurate blood tests.

In a cross-examination of the evidence given by Professor A. Weetman by the General Medical Council’s barrister at a recent Fitness to Practice Hearing , when asked…

> ***Q**. You say at 7.2: "[A] pertinent aspect in this discussion is the definition of the reference range for TSH." You talk about the laboratory tests and then you talk about: "In simple terms this means that 95 % of normal values will lie within the reference range, 2.5 % will lie below it and 2.5 % above it. This is why the term reference range is preferred to 'normally (sic) range'." Now the reference range that we are now talking about is not the goal, as it were, of treatment that we were talking about earlier?*
>
> ***A.** "No, as I have said, the recommendations most recently made by the BTA and the clinical biochemists is that one should simply bring the TSH to within the reference range, and **I have indicated that personally (and a number of other endocrinologists would do the same) confronted with a patient who continued to have symptoms despite bringing the TSH down to three - I would bring it down further still**.* (103)

This is a hint that since the patient is not better on the treatment, that there is something else wrong, as mentioned above. No possibility exists, apparently, for there to be anything wrong with the dosage or support medication - it has to be something else. As we have indicated above, many factors may influence response to treatment; adrenal insufficiency, hormonal imbalances, food allergies, systemic candidiaisis, low serum ferritin, low B12, low Vitamin D, low magnesium, copper or zinc – or simply the patient is unable, for one reason or another, to convert T4 into T3.

It would be helpful if the RCP could let doctors know which blood tests are recommended as relevant to the symptoms of Hypothyroidism, if tests for Hypothyroidism come back as biochemically normal.

Conditions or factors that depress serum TSH are aging, (3,4) fasting, (5-8) strenuous physical activity,(8) pregnancy,(9) depression and anxiety disorders,(11 -15) Non-thyroidal diseases: diabetes mellitus, Cushing's syndrome, renal failure, cancer, myocardial infarction, AIDS, post-traumatic syndromes, chronic alcoholic liver disease, other illnesses,(16-32) Medications: thyroid therapy, estroprogestative birth control pills, progestogens, anti-infammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptica, anti-hypertensives, antiarrhythmics (amiodarone), hypolipemic agents, IGF-1, somatostatin, etc.(33-51) toxic foods: MSG, alcohol,(52-54) Thyroid diseases: hyperthyroidism, Graves-Basedow disease, nodular goiter, thyroiditis, secondary or tertiary hypothyroidism, congenital hypothyroidism,(55-57)

Factors that elevate TSH are: Neonatus, stress - emotional arousal, cold exposure, sleep deprivation, adrenal insufficiency, recovery from severe illness, congenital malformations,(60-67) Medications: iodine, antithyroidea, lithium, neuroleptica (haloperidol, chlorpromazine), cimetidine, sulfapyridine, clomifen, antidepressants (sertraline), antihistaminic agents, cholestograhic agents, etc.(68-71) Auto-immune thyroiditis and hypothyroidism: primary, iodine-deficient, thyroid hormone resistance,(72-76) TSH-secreting tumours (rare),(77). There are also many factors that depress and elevate serum TSH: Physiological serum TSH fluctuations, (78-84) variations in the biological activity of TSH, (85-87). There are, of course, TSH test kit imperfections, (88-102)

References:

1. *William Winter and Neil Harris, A New Type of Thyroid Disease, Advance for Administrators of the Laboratory, June, 2008: 46-50.*
2. *Sapin R. [Interferences in immunoassays: Mechanisms and outcomes in endocrinology] Ann Endocrinol (Paris). 2008 Nov; 69(5):415-25. Epub 2008 Jun 5.*
3. *Urban RJ. Neuroendocrinology of aging in the male and female. Endocrinol Metab Clin North Am. 1992;21(4): 921-31*
4. *Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991; 151(1): 165-8*
5. *Croxson MS, Hall TD, Kletzky OA, Jaramillo JE, Nicoloff OA. Decreased serum thyrotropin induced by fasting. J Clin Endocrinol Metab. 1977; 45: 560*
6. *Borst GC, Osburne RC, O'Brian JT, Georges LP, Burman KD. Fasting decreases thyrotropin responsiveness to thyrotropin-releasing hormone: A potential cause of misinterpretation of thyroid function tests in the critically ill. J Clin Endocrinol Metab. 1983 Aug;57(2):380-3*

7. *Campbell GA, Kurcz M, Marshall S, Meites J. Effects of starvation in rats on serum levels of follicle stimulating hormone, luteinizing hormone, thyrotropin, growth hormone and prolactin; response to LH-releasing hormone and thyrotropin-releasing hormone. Endocrinology. 1977; 100(2): 580-7*
8. *Opstad PK. The thyroid function in young men during prolonged physical stress and the effect of energy and sleep deprivation. Clin Endocrinol. 1984; 20: 657-69.*
9. *Scanlon MF, Toft AD. Regulation of thyrotropin secretion. In Werner and Ingbar's The Thyroid, 7th edition*
10. *Braverman LE and Utiger RE, Lippincott-Raven Publisers, Philadelphia. 1996; 220-40.*
11. *Bartalena L, Placidi GF, Martino E, Falcone M, Pellegrini L, Dell'Osso L, Pacchiarotti A, Pinchera A. Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: dissociated behavior in untreated depressives. Clin Endocrinol Metab. 1990 Sep;71(3):650-5.*
12. *Rupprecht R, Rupprecht C, Rupprecht M, Noder M, Mahlstedt J. Triiodothyronine, thyroxine, and TSH response to dexamethasone in depressed patients and normal controls. Biol Psychiatry. 1989;25(1): 22-32.*
13. *Maeda K, Yoshimoto Y, Yamadori A. Blunted TSH and unaltered PRL responses to TRH following repeated administration of TRH in neurological patients: A replication of neuroendocrine features of major depression. Biol Psychiatry. 1993; 33(4): 277-83.*
14. *Duval F, Macher JP, Mokrani MC. Difference between evening and morning thyrotropin responses to protirelin in major depressive episode. Arch Gen Psychiatry. 1990; 47(5): 443-8.*
15. *Loosen PT, Prange AJ Jr. erum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: A review. Am J Psychiatry 1982; 139(4): 405-16.*
16. *Devos P. Rationele keuze van schildklierfunctie tests. Tijdschr Geneesk. 1990; 46(8): 591-9*
17. *Alexander CM, Kaptein EM, Lum SMC, Spencer CA, Kumar K, Nicoloff JT. Pattern of recovery of thyroid hormone indices associated with treatment of diabetes mellitus. J Clin Endocrinol Metab. 1982; 54: 362-366*
18. *Andrade SF, Kanitz-Ml, Povoa H Jr. Study of thyrotropic reserve in diabetics of adult type. Acta-Biol Mod Ger 1977; 36(10): 1479-81*
19. *Gonzalez C, Montoya-E, Jolin T. Effect of streptozotocin diabetes on the hypothalamic pituitary thyroid axis in the rat. Endocrinology 1980; 107(6): 2099-103*
20. *Rossi GL, Bestetti GE, Tontis DK, Varini M. Reverse hemolytic plaque assay study of luteinizing and follicle-stimulating hormone and thyrotropin secretion in diabetic rat pituitary glands. Diabetes 1989; 38(10): 1301-6*
21. *Adriaanse R, Brabant G, Endert E, Wiersinga W. Pulsatile thyrotropin secretion in patients with Cushing's syndrome. Metabolism. 1994 Jun;43(6):782-6*
22. *Beyer HK-, Schuster P, Pressler H. Studies on hypothalamic pituitary thyroid regulation in hemodialysis patients. Nuklearmedizin 1981;20(1):19-24*
23. *Kokei S, Inoue T, lino S. Serum free thyroid hormones and response of TSH to TRH in nonthyroidal illnesses. Nippon Naibunpi Gakkai Zasshi. 1986; 62(11): 1231-43*
24. *De Marinis L, Mancini A, Masala R, Torlontano M, Sandric S, Barbarino A. Evaluation of pituitary-thyroid axis response to acute myocardial infarct. J Endocrinol Invest. 1985; 8(6): 519-22*
25. *Rondanelli M, Solerte SG, Fioravanti M, Scevola K, et al. Circadian secretory pattern of growth hormone, insulin-like growth factor type I, cortisol, adrenocorticotropic hormone, thyroid-stimulating hormone, and prolactin during HIV infection. AIDS Res Hum Retroviruses. 1997; 13(14): 1243-9.*
26. *Wintemitz WW, Dzur JA. Pituitary failure secondary to head trauma. Case report. J Neurosurg. 1976; 44(4): 504-5*
27. *Dzur JA, Wintemitz WW. Posttraumatic hypopituitarism: Anterior pituitary insufficiency secondary to head trauma. South Med J. 1976; 69(10): 1377-9*
28. *Modigliani E, Periac P, Perret G, Hugues JN, Coste T. TRH response in 53 patients with chronic alcoholism. Ann Med Interne Paris. 1979; 130(5):297-302*
29. *Ekman AC, Vakkuri 0, Ekman M, Leppalusto J, Ruckonen A, Knip M. Ethanol decreases nocturnal plasma levels of thyrotropin and growth hormone but not those of thyroid hormones or protection in man. J Clin Endocrinol Metab. 1996; 81(7):2627-32*
30. *Bacci V, Schussler GC, Kaplan TB. The relationschip between serum triidothyronine and thyrotropin during systemic illness. J Clin Endocrinol Metab. 1982; 54:1229-35*
31. *Hamblin PS, Dyer SA, Mohr VS, Le Grand BA, Lim CF, Tuxen DV, Topliss DJ, Stockigt JR. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. J Clin Endocrinol Metab. 1986 Apr;62(4):717-22*
32. *Bermudez F, Sucks MI, Opperheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab. 1975; 41: 27-40.*
33. *Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab. 1994;78(6):1368-71*
34. *Gow SM, Caldwell G, Toft AD, Seth J, Hussey AJ, Sweeting VM, Beckett GJ. Relationship between pituitary and other target organ responsiveness in hypothyroid patients receiving thyroxine replacement. J Clin Endocrinol Metab. 1987;64(2):364-70*
35. *Custro N, Scafidi V Costanzo G, Corsello FP. Variations in the serum levels of thyroid hormones and TSH after intake of a dose of L-thyroxine in euthyroid subjects and in adequately treated hypothyroid patients. Bull Soc Ital Biol Sper. l989; 65(11):1045-52*

36. *England ML, Hershman JM. Serum TSH concentration as an aid to monitoring compliance with thyroid hormone therapy in hypothyroidism. Am J Med Sci. 1986 Nov;292(5):264-6*
37. *Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3,',5'-triiodothyronine (rT3,), and 3,3'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978; 103(2): 393-402*
38. *Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? Br Med J (Clin Res Ed). 1986 Sep 27;293(6550): 293-808*
39. *Cooper DS, Walker H, Rodbard D, Maloof F. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 1981 Dec;53(6):1238-42*
40. *Saberi M, Utiger RD. Serum thyroid hormone and thyrotropin concentrations during thyroxine and triiodothyronine therapy. J Clin Endocrinol Metabol. 1974;39:923-7*
41. *Rey Stocker I, Zufferey MM, Lemarchand MT, Rais M. The sensibility of the hypophysis, the gonads and the thyroid before and after the administration of oral contraceptives. A resume. Pediatr Ann. 1981;10(12):15-20.*
42. *Lemarchand-Beraud T. Influence of estrogens on pituitary responsiveness to LHRH and TRH in human. Reymond M, Berthier C. Ann Endocrinol Paris. 1977; 38(6): 379-82.*
43. *El-Etreby MF, Graf KJ, Gunzel P, Neumann F. Evaluation of effects of sexual steroids on the hypothalamic-pituitary system of animals and man. Arch Toxicol Suppl. 1979;2:11-39*
44. *Prank K, Ranft U, Bergmann P, Schuermeyer T, Hesch RD, von Zur Muhlen A. Circadian and pulsatile TSH secretion under physiological and pathological conditions. Horm Metab Res Suppl. 1990; 23:12-7*
45. *Re RN, Kourides IA, Ridgeway EC, Weintraub BD, Maloof F. The effect of glucocorticoid administation on human pituitary secretion of thyrotropin and prolactin. J Clin Endocrinol Metab. 1976; 43:338-46.*
46. *Atterwill CK, Catto LC, Heal DJ, Holland CW, Dickens TA, Jones CA. The effects of desipramine (DMI) and electroconvulsive shock (ECS) on the function of the hypothalamo-pituitary-thyroid axis in the rat. Psychoneuroendocrinology. 1989;14(5):339-46*
47. *Kaptein EM, Kletzsky OA, Spencer CA, NicoloffJT. Effects of prolonged dopamine infusion on anterior pituitary function in normal males. J Clin Endocrinol Metab 1980; 51:488-91*
48. *Samuels MH, Kramer P, Wilson D, Sexton F. Effect ofnaloxone infusions on pulsatile thyrotropin secretion. J Clin Endocrinol Metab. 1994;78(5):129-32.*
49. *Burger A, Nicod DP, Lemarchaud-Beraud T, Vallotton MB. Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxine and thyrotropin. J Clin Invest 1976; 58: 255-9*
50. *Davis PJ, Davis FB, Utiger RD, Kulaga SF Jr. Changes in serum thyrotropin (TSH) in man during halofenate administration. J Clin Endocrinol Metab 1976; 43(4): 873-81*
51. *Trainer PI, Holly 1, Medbak S, Rais LH, Besser GM. The effect of recombinant IGF-1 on anterior pituitary function in healthy volunteers. Clin Endocrinol (Chef) 1994; 41(6): 801-7.*
52. *Bakke JL, Lawrence N, Bennett J, Robinson S, Bowers CY. Late endocrine effects of administering monosodium glutamate to neonatal rats. Neuroendocrinology 1978; 26(4): 220-8.*
53. *Greeley GH Jr, Nicholson GF, Kizer JS. A delayed LH/FSH rise after gonadectomy and a delayed serum TSH rise after thyroidectomy in monosodium-L-glutamate (MSG)-treated rats. Brain Res 1980; 195(1):111-22*
54. *Modigliani E, Periac P, Perret G, Hugues JN, Coste T. TRH response in 53 patients with chronic alcoholism. Ann Med Interne Paris. 1979; 130(5): 297-302*
55. *Spencer CA, Lai-Rosenfeld AO, Guttler RB, LoPresti J, Marcus AO, Nimalasuriya A, Eigen A, Doss RC, Green BJ, Nicoloff JT. Thyrotropin secretion in thyrotoxic and thyroxine-treated patients: assessment by a sensitive immunoenzymometric assay. J Clin Endocrinol Metab. 1986 Aug;63(2):349-55*
56. *Yeo PP, Loh KC. Subclinical thyrotoxicosis. Adv Intern Med. 1998; 43: 501-32*
57. *Chanson P. Insuffisance thyrotropic. Rev Prat. 1998 15; 48(18): 2023-6*
58. *Petersen PH, RosleffF, Rasmussen J, Hobolth N. Studies on the required analytical quality of TSH measurements in screening for congenital hypothyroidism. Scand J Clin Lab Invest Suppl. 1980;155: 5-93.*
59. *Fofanova 0V, Takamura N, Kinoshita E, Yoshimoto M, Tsuji Y, Peterkova VA, Evgrafov 0V, Dedov II, Goncharov NP, Yamashita S. Rarity of PIT1 involvement in children from Russia with combined pituitary hormone deficiency. Am J Med Genet 1998; 77(5): 360-5.*
60. *Hashimoto H, Sato F, Kubo M, Ohki T. Maturation of the pituitary-thyroid axis during the perinatal period. Endocrinol Jpn 1991;38(2):151-7*
61. *Gendrel D, Feinstein MC, Grenier J, Roger M, Ingrand J, Chaussain JL, Canlorbe P, Job JC. Falsely elevated serum thyrotropin (TSH) in newborn infants: Transfer from mothers to infants of a factor interfering in the TSH radioimmunoassay. J Clin Endocrinol Metab 1981;52(1):62-5.*
62. *Armario A, Lopez Calderon A, Jolin T, Castellanos JM. Sensitivity of anterior pituitary hormones to graded levels of psychological stress. Life Sci 1986; 39(5): 471-5*
63. *Reed HL, Silverman ED, Shakir KM, Dons R, Burman KD, O'Brian JT. Changes in serum triiodothyronine (TQ kinetics after prolonged Antarctic residence: The polar T3 syndrome. J Clin Endocrinol Metab. 1990; 70(4): 965-74*
64. *Sadamatsu M, Kato N, Iida H, Takahashi S, Sakaue K, Takahashi K, Hashida S, Ishikawa E. The 24-hour rhythms in plasma growth hormone, prolactin and thyroid stimulating hormone: effect of sleep deprivation. J Neuroendocrinol. 1995 Aug;7(8):597-606*
65. *Sjoberg S, Wemer S. Increased level of TSH can be a sign of adrenal cortex failures: Not necessarily of thyroid gland disease. Lakartidningen 1999; 96(5):464-5*

66. *De Nayer P, Dozin B, Vandeput Y, Bottazzo FC, Crabbe J. Altered interaction between triiodothyronine and its nuclear receptors in absence of cortisol: A proposed mechanism for increased thyrotropin secretion in corticoid deficiency states. Eur J Clin Invest. 1987 Apr;17(2):106-8*
67. *Oakley GA, Muir T, Ray M, Girdwood RW, Kennedy R, Donaldson MD. Increased incidence of congenital malformations in children with transient thyroid-stimulating hormonal elevation on neonatal screening. J Pediatr. 1998; 132(4): 573-4*
68. *Devos P. Rationele keuze van schildklierfunctie tests. Tijdschr Geneesk. 1990;46(8):591-9*
69. *Kleinmann RE, Vagenakis AG, Braverman LE. The effect of iopanoic acid on the regulation of thyrotropin secretion in euthyroid subjects. J Clin Endocrinol Metab. 1980;51(2): 399-403*
70. *Mc Caven KC, Garber JR, Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. N Engl J Med. 1997; 337(14):1010-1*
71. *Brown CG, Harland RE, Major IR, Atterwill CK. Effects of toxic doses of a novel histamine (H2) antagonist on the rat thyroid gland. Food Chem Toxicol. 1987; 25(10):787-94*
72. *Devos P. Rationele keuze van schildklierfunctie tests. Tijdschr Geneesk. 1990;46(8): 591-9*
73. *Missler U, Gutekunst R, Wood WG. Thyroglobulin is a more sensitive indicator of iodine deficiency than thyrotropin: Development and evaluation of dry blood spot assays for thyrotropin and thyroglobulin in iodine- deficient geographical areas. Eur J Clin Chem Clin Biochem 1994; 32(3): 137-43*
74. *Volpe R. Subacute (de Quervain's) thyroiditis. J Clin Endocrinol Metab. 1979 Mar;8(1):81-95*
75. *Massoudi MS, Meilahn EN, Orchard TJ, Foley TP Jr, Kuller LH, Costantino JP, Buhari AM. Thyroid function and perimenopausal lipid and weight changes: the Thyroid Study in Healthy Women (TSH-W). J Womens Health. 1997 Oct;6(5):553-8*
76. *Smallridge RC, Parker RA, Wiggs EA, Rajagopal KR, Fein HG. Thyroid hormone resistance in a large kindred: physiologic, biochemical, pharmacologic, and neuropsychologic studies. Am J Med. 1989 Mar;86(3):289-96*
77. *Smallridge RC. Thyrotropin-secreting pituitary tumors, Endocrinol Metab Clin North Am 1987 Sep;16(3):765-92*
78. *Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B, Feistner H, Hesch RD, von zur Muhlen A. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. J Clin Endocrinol Metab. 1990 Feb;70(2):403-9*
79. *Brabant G, Prank K, Ranft U, Bergmann P, Schuermeyer T, Hesch RD, von zur Muhlen A. Circadian and pulsatile TSH secretion under physiological and pathophysiological conditions. Horm Metab Res Suppl. 1990;23:12-7*
80. *Goichot B, Brandenberger G, Schlienger JL. Secretion of thyrotropin during states of wakefulness and sleep. Physiological data and clinical applications. Presse Med. 1996;25(21):980-4*
81. *Rao ML, Gross G, Strebel B, Halaris A, Huber G, Braunig P, Marler M. Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. Biol Psychiatry. 1994;1:35(3): 151-63*
82. *Rose SR, Nisula BC. Circadian variation of thyrotropin in childhood. J Clin Endocrinol Metab. 1989; 68(6):1086-90*
83. *Scanlon MF, Weetman AP, Lewis M, Pourmand M, Rodriguez Arnao MD, Weightman DR, Hall R. Dopaminergic modulation of circadian thyrotropin rhythms and thyroid hormone levels in euthyroid subjects. J Clin Endocrinol Metab. 1980 Dec;51(6):1251-6*
84. *Rom Bugoslavskaia ES, Shcherbakova VS. Seasonal characteristics of the effect of melatonin on thyroid function. Bull Eksp Biol Med. 1986;101(3):268-9*
85. *Beck-Peccoz P, Persani L. Variable biological activity of thyroid stimulating hormone. Eur J Endocrinol. 1994 Oct;131(4):331-40*
86. *Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, De Meyer F, Scharpe S. Components of biological variation of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. Clin Endocrinol (Oxf). 1997 May;46(5):587-98*
87. *Hiromoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: Comparison between the in vivo 3,5,3'- triiodo-thyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab. 1995 Apr;80(4):1124-8*
88. *Rasmussen AK, Hilsted L, Perrild H, Christiansen E, Siersbaek-Nielsen K, Feldt-Rasmussen U. Discrepancies between thyrotropin (TSH) meaasurement by four sensitive immunometric assays. Clin Chim Acta. 1997 Mar 18;259(1-2):117-28*
89. *Libeer JC, Simonet L, Gillet R. Analytical evaluation of twenty assays for determination of thyrotropin (TSH). Ann Biol Clin Paris. 1989; 47(1): 1-11*
90. *Spencer CA, Takeuchi M, Kazarosyan M, MacKenzie F, Beckett GJ, Wilkinson E. Interlaboratory/intermethod differences in functional sensitivity of immunometric assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. Clin Chem. 1995 Mar;41(3):367-74*
91. *Faber J, Gam A, Siersbaek Nielsen K. Improved sensitivity of serum thyrotropin measurements: Studies on serum sex hormone-binding globulin in patients with reduced serum thyrotropin. Acta Endocrinol Copenh 1990; 123(5): 535-40*
92. *Laurberg P. Persistent problems with the specificity of immunometric TSH assays. Thyroid. 1993 Winter;3(4):279-83*
93. *Schlienger JL, Sapin R, Grunenberger F, Gasser F, Pradignac A. Thyrotropin assay by chemiluminescence in the diagnosis of dysthyroidism with low thyrotropin and normal thyroid hormones levels. Pathol Biol Paris. 1993; 41(5): 463-8*
94. *Spencer C, Eigen A, Shen D, Duda M, Qualls S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem. 1987 Aug;33(8):1391-6*
95. *Spencer CA, Challand GS. Interference in a radioimmunoassay for human thyrotropin. Clin Chem 1977;23(3): 584-8*
96. *Kahn BB, Weintraub BD, Csako G, Zweig MH. Factitious elevation of thyrotropin in a new ultra-sensitive assay: Implications for the use of monoclonal antibodies in 'sandwich' immuno-assay. J Clin Endocrinol Metab. 1988 Mar;66(3):526-33*

97. *Kourides IA, Weintraub BD, Martorana MAL, Maloof F. Alpha subunit contamination of human albumin preparations: Interference in radioimmunoassay. J Clin Endocrinol Metab. 1976; 43(4): 919-23*
98. *Bartlett WA, Browning MC, Jung RT. Artefactual increase in serum thyrotropin concentration caused by heterophilic antibodies with specificity for IgG of the family Bouidea. Clin Chem. 1986; 32(12): 22(4-9)*
99. *Csako G, Weintraub BD, Zweig MH. The potency of immunoglobulin antibodies in a monoclonal immunoradiometric assay for thyrotropin. Clin Chem. 1988 Jul;34(7):1481-3*
100. *Seghers J, Schruers F, De Nayer P, Beckers C. Interference in thyrotropin (TSH) determination: Falsely elevated TSH values in a transplanted patient. Eur J Nucl Med. 1989; 15(4): 194-6*
101. *Spencer C, Eigen A, Shen D, Duda M, Quails S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem. 1987;33(8):1391-6*
102. *Ealey PA, Marshall NJ, Ekins RP. Time-related thyroid stimulation by thyrotropin and thyroid-stimulating antibodies, as measured by the cytochemical section bioassay. J Clin Endocrinol Metab. 1981;52(3): 483-7*
103. *Thyroid Patient Advocacy-UK. "Dr Gordon Skinner General Medical Council Hearing Transcripts" http://www.tpa-uk.org.uk/skinner_hearing_transcripts.php .pp19*

To be commended…

> *The RCP state that they recognise that different test methods can give different results and they support the international initiative for greater harmonisation of reference ranges and of the units used in expressing results.*

…however we learn from elsewhere in the RCP 'guideline' that other tests are <u>not</u> recognised without "clinical validation"; and other "body fluids" are similarly <u>not</u> recognised. So this statement is meaningless.

Competing interests

> *The RCP state that "when a sufficient dose of thyroid treatment is given to lower the TSH to the normal range for the test method used, patients usually lose their symptoms of hypothyroidism."*

The problem here is the use of the word "usually". Often patients do lose these symptoms - but often they don't. What then is the RCP recommendation? This statement is entirely unhelpful.

It is this false belief that has led to "new diseases" of the past 30 years. These new diseases are so-called "fibromyalgia" and "chronic fatigue syndrome." A vast amount of evidence indicates that inadequate thyroid hormone regulation is the major underlying causative factor in these supposed new disorders. For example, the only studies in which patients with these diagnoses have fully and lastingly recovered, are those in which they underwent thyroid hormone therapy replacement.(1-9)

The RCP's view that levothyroxine is the "treatment of choice" for hypothyroidism brought to mind an article: "The Tomato Effect: Rejection of highly efficacious therapies" (*JAMA* 1984).(10) New settlers in America refused to eat tomatoes as they belonged to the "nightshade family" and were thought to be poisonous despite evidence to the contrary! This article describes how highly effective therapies are abandoned due to paradigm shifts in the way physicians think about health and disease. An explanation of how 'the tomato effect' could influence the treatment of hypothyroidism is given in a Lancet editorial.(11)

There are many researchers, doctors, and patient advocates who believe that the BTA has been obstinate in its advocacy of thyroxine-only therapy. TPA-UK is concerned that the obduracy of the BTA may be linked, as they are now a registered charity, to the possibility that they may receive regular financial support from drug companies who profit from the prescribing of synthetic thyroxine. This suspicion of financial motivation is reinforced by the BTA's standard method of enforcing the practice of synthetic thyroxine-only therapy among doctors: dictatorship replacing scientific argument and debate. The suspicion will continue to mount if the BTA, despite the studies showing replacement therapies to be ineffective,(12-17) even harmful (18,19) for many sufferers, continue to ignore the existing evidence demonstrated in this paper by TPA-UK.

The influence of drug companies creates anxiety, insecurity, a lack of trust plus a loss of integrity between doctors and patients. Watching the fear, uncertainty and doubt being actively propagated by vested interests, is frustrating, disappointing and harmful for the patient.

All aspects of patient care can be open to manipulation and this appears to be a very insidious problem, especially for sufferers of hypothyroidism.

The BTA, in partnership with the BTF and the ACB have drawn up, and maintain “The UK Guidelines for The Use of Thyroid Function Tests”.(20) This imposes a great responsibility upon them to protect hypothyroid patients from adverse consequences. That responsibility is the compelling reason for the RCP to promptly reform its incorrect official position that thyroxine-only replacement is safe and effective for *all* hypothyroid patients.

The real tragedy is the still unmeasured cost in terms of patient’s quality of life and the consequential massive burden placed on State resources, both for the NHS and the Treasury. The RCP ‘guidelines’ are not compatible with Science and Integrity. It appears that whatever the BTA decides to ‘recommend’ it does so by stealth and by definition, under the guise of “acting as an expert”. The professional integrity of any independent organisation is compromised and the trust of the patient is betrayed. The doctor patient-relationship has failed.

To those doctors we recommend that they listen to, and investigate, the claims from all with an open mind, questioning the veracity of the ‘scientific evidence’ presented, before acting on any existing treatment as recommended in this guideline. This process is invisible to patients, so we have to rely on the doctors’ integrity.

To quote just one patient:

> *“The ignorance, arrogance and incomprehension of the medical doctors I have been subjected to in my search for diagnosis and treatment leaves me incandescent with rage. Even as a qualified health professional working for a major DGH I remain powerless to prevent the cumulative long term health risks associated with lack of treatment; I am voiceless, neutered, patronised, and crawling day-to-day through what used to be my vital and colourful life. I would give everything I have for an open minded and creative diagnostician, and more for a little compassion, but this seems to be entirely beyond the capability of the modern medic. God help us all.”(21)*

References :

1. *Lowe, J.C., Garrison, R., Reichman, A., Yellin, J., Thompson, M., and Kaufman, D. .”Effectiveness and safety of T3 therapy for euthyroid fibromyalgia: a double-blind, placebocontrolled response-driven crossover study.” Clin. Bull. Myofascial Ther., 1997, 2(2/3):31-57*
2. *Lowe, J.C., Garrison, R., Reichman, A., and Yellin, J. ”Triiodothyronine (T3) treatment of euthyroid fibromyalgia: a small-n replication of a double-blind placebo-controlled crossover study.” Clin. Bull. Myofascial Ther., 1997, 2(4):71-88. 116.*
3. *Lowe, J.C., Reichman, A., and Yellin, J. ”The process of change with T3 therapy for euthyroid fibromyalgia: a double-blind placebo-controlled crossover study.” Clin. Bull. Myofascial The1997, 2(2/3):91-124.*
4. *Teitelbaum, J., Bird, B., Greenfield, R.M., et al. ”Effective treatment of CFS and FMS: a randomized, double-blind placebo controlled study.” J. Chron. Fatigue Synd., 2001, 8(2):3-28*
5. *Skinner, G.R.B., Holmes, D., Ahmad, A., Davies, A., and Benitez, J. ”Clinical response to thyroxine sodium in clinically hypothyroid but biochemically euthyroid patients.” J. Nutri. Environ. Med., 2000, 10:115-124.*
6. *Lowe, J.C. ”T3-induced recovery from fibromyalgia by a hypothyroid patient resistant to T4 and desiccated thyroid.” J. Myofascial Ther., 1995, 1(4):26-31.*
7. *Lowe, J.C. ”Results of an open trial of T3 therapy with 77 female euthyroid fibromyalgia patients. ” Clin. Bull. Myofascial Ther., 1997, 2(1):35-37.*
8. *Honeyman, G.S. ”Metabolic therepy for hypothyroid and euthyroid fibromyalgia; two case reports. ” Clin. Bull. Myofascial Ther., 1997, 2(4):19-49.*
9. *Carr, C., McLeod, D.T., Parry, G., et al. “Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin asswith measurement of free thyroid hormones and clinical*

assessment." Clin. Endocrinol., 128:325-333.

10. *Goodwin J.S. "The Tomato Effect. Rejection of Highly Effecacious Therapies" . JAMA 1984;251 (18);2387-90*
11. *"Drug-complany influence on medical education in USA", Lancet 2000; 356(9232):78*
12. *Bhagat MC, Cussons AJ. "Combined thyroxine/liothyromine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism." J Clin Endocrinol Metab 88:4543–4550, 2003.*
13. *Sawka A. M., Gerstein H.C., Marriott M.J., MacQueen G.M., Joffe R.T. "Does a combination regimen of thyroxine (T4) and 3, 5, 3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial." J Clin Endocrinol Metab 88:4551–4555, 2003.*
14. *Clyde, P.W., Harari, A.E., Getka, E.J., and Shakir, K.M.M. "Combined levothyroxliothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial." JAMA, 2003, 290:2952-2958*
15. *Cassio, A., Cacciari, E., Cicgnani, A., et al. "Treatment of congenital hypothyroidism: thyroxine alone or thyroxine plus triiodothyronine?" Pediatrics, 2003,111(5):1055-1060*
16. *Bunevicius R., Kazanavicius G., Zalinkevicius R., Prange A.J. Jr., Institute of EndocrinologyKaunas Medical University, Lithuania. "Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothoidism.*
17. *Bunevicius R., Jakubonien N., Jurkevicius R., Cernicat J., Lasas L., Prange A.J., InstEndocrinology, Clinic of the Kaunas Medical University, Lithuania. "Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease." Endocrine, July 18 2002; (2):129-33.*
18. *Perk, M. and O'Neill, B.J. "The effect of thyroid hormone therapy on angiographic coronary artery disease progression." Can. J. Cardiol., 13(3):273-276, 1997.*
19. *Saravanan, P., Chau,W.F. Roberts, N. et al. "Psychological well-being in patients on 'adequate' doses of L-thyroxine: Results of a large, controlled community-based questionnairstudy." Clin. Endocrinol. (Oxf.), 2002, 57(5):577-585.*
20. *"The UK Guidelines for the Use of Thyroid Function Tests" British Thyroid Association of Clinical Biochemists, British Thyroid Foundation, July 2006. http://www.british-thyroid association.org/TFT_guideline_final_version_July_2006.pdf*
21. *"Patients' Petition for Better Diagnosis and Treatment Choice for Hypothyroid Patients," International Hormone Society http://intlhormonesociety.org/index.php?option=com_content&task=view&id=31&Itemid=53&tomHack_idp=10*

A monumental deceit – Is Big Pharma paying the piper?

PART 1 (Synthetic T4-T3 therapy)

> *The RCP state "Overwhelming evidence supports the use of Thyroxine (T4) alone in the treatment of hypothyroidism. Thyroxine is usually prescribed as levothyroxine. We do not recommend the prescribing of additional Tri-iodothyronine (T3) in any presently available formulation…."*

It is this statement which seeks to bludgeon into the clinician the establishment line, by repeating the standard belief often enough and loud enough. The logicality of T4 alone has been commented on above; and to suggest that the use of any other approach is inconsistent with normal physiology is totally and demonstrably wrong. Overwhelming evidence supports the use of synthetic T4/T3 and natural thyroid extract. The RCP may not recommend the use of T3; but that is how nature does it - and this cannot be denied. Having an adequate supply of T3 present during all phases of initiating treatment forestalls the build-up of L-thyroxine that produces the storm.

Natural desiccated thyroid is almost an exact copy of the body's thyroid production, with T4, T3, T2, T1 and calcitonin. It has been used safely and effectively for over 100 years, and if doctors listened to their patients instead of the drug companies selling levothyroxine, they would know it works better by far than their patentable, synthetic, thyroxine.

Since desiccated thyroid delivers all of the thyroid related hormones, and levothyroxine is a virtually pure thyroxine replacement, the other thyroid related hormones must be doing something for some patients. Nonetheless, the entrenched hypothyroidism paradigm still refuses to recognise the possibility for any other thyroid related hormone operation between the thyroid and the symptom producing cells. The discoveries by medical science in 1967 and 1970 of resistance to thyroid hormone reception by the peripheral cells and of the peripheral conversion of T4 to T3 have not changed this paradigm. However, they do explain the continuing symptoms and the need for T3-containing hormone replacements.

Rather than the RCP denouncing T3 therapy, they would better serve their patients' welfare by reading the relevant studies and then rectifying their judgment of T3 to reflect its safety and the potential benefits for select patients. The view that hypothyroidism is best treated by thyroxine alone is not, and never has been, based on solid scientific evidence. To this end, the effectiveness of whole thyroid extract versus synthetics should be compared in further clinical trials, especially involving problematic patients – as was first shown in a 1932 study comparing levothyroxine and desiccated thyroid extract in hypothyroid patients.(1) There have since been at least a further thirteen studies directly comparing desiccated thyroid to levothyroxine alone.(2-14)

The Royal College and BTA et al should read the Yellow Card reports that accompany the last 40 plus years of grossly under-reported adverse events on levothyroxine only.(15)
There is no such data for Armour Thyroid, USP.

Dr. E. Chester Ridgway wrote…

> *"T4 . . . is not the active ingredient. T3 is the active ingredient and it's the thing that accounts for the thyroid hormone action. As I've been reminded many times, there are no intracellular events that we know that can be described by T4 at the level of the nucleus. Only T3. T4 is not the active compound. Likewise, the site of action is in the nucleus. The site of action is not T4 in the plasma." (*16)

The MHRA granted Goldshield Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Liothyronine Sodium 20 microgram Injection on 8th October 2007. This product, to be available by prescription only (POM), contains liothyronine sodium and is used for the treatment of severe thyroid gland deficiency (myxoedema), when it is not possible to give thyroid treatment by mouth.
GI problems with absorption or liver disease would include this aspect, and especially if a GP could not differentiate thyroidal from non-thyroidal illness.(17)

This application is a duplicate of a previously granted application for Triiodothyronine Injection 20 micrograms (PL 10972/0040) containing liothyronine as active ingredient, for which the marketing authorisation holder is Goldshield Group Plc and which was first authorised on 23rd August 1993.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Liothyronine Sodium 20 microgram Injection outweigh the risks; hence a Marketing Authorisation has been granted.

It would have been beneficial to medical practitioners and patients had the RSP cited references to their "overwhelming evidence" to support the use of synthetic T4 alone. There is overwhelming evidence to support the use of synthetic T4/T3, T3-only, or natural thyroid extract, Armour Thyroid, USP.

The International Hormone Society, currently the third largest international endocrine society with over 2000 physician members worldwide, has published a consensus on thyroid treatment that includes T4-only preparations, combinations of synthetic and natural (Armour),synthetic T3/T4 and T3-only therapy, whichever is in the best interest of the patient.(18) The consensus is supported by much scientific evidence, and over 2000 signatures from physicians have been received supporting this consensus.(19)

Further evidence of patients' dissatisfaction with T4 only therapy can be seen on the 'International Thyroid Patients' Petition for Better Diagnosis and Treatment Choice for Hypothyroid Patients'.(20)

The studies comparing the efficacy of thyroxine alone versus combination T4/T3 preparations have in general not shown superiority of T4 alone above the combination of T4 with a smaller dose of T3. On the contrary, a few studies have shown a significantly greater efficacy of combined T4/T3 medications compared to the use of T4 alone in humans on such divergent parameters as serum cholesterol, mental and physical symptoms, and in animals on goitre formation and intracellular T3 - euthyroidism, just to name some of the greater benefits. T3 is the major intracellular thyroid hormone, and a low serum level

of T3 occurs more often than a low serum T4 or a high TSH, the critical parameter in mortality studies, especially cardiovascular, and the absorption of T3 is much more efficient and stable than that of T4 alone, which gives credibility to the view that a combination of T4 with T3 may be better for the hypothyroid patient.

Despite the studies showing replacement therapies to be ineffective, (21-26) even harmful (27, 28) for many sufferers, the RCP need to declare why they choose to ignore the existing evidence demonstrated in this paper.

In the study conducted by Bunevecius et al 1999, combined thyroxine / liothyronine treatment was shown to be superior to thyroxine mono-therapy in terms of mood and neuropsychological function in a group of 17 thyroid cancer patients and 16 chronic autoimmune thyroiditis patients(29). In a follow-up study (30) patients treated for thyroid cancer showed more mental improvement than those with autoimmune thyroiditis, possibly because the thyroid cancer patients were more dependent on exogenous thyroid hormone and were therefore receiving higher dosages. Subsequently a number of studies failed to reveal any benefit for combined therapy. (21-24)

However, it must be noted that the patients in these studies received low doses of thyroid hormone, titrated according to TSH level, a poor marker for thyroid hormone tissue response. Other studies have shown that treatment with T4 only does not succeed in achieving complete cellular euthyroidism in the target organs (29,30) probably because T3 is really the active hormone, and studies of thyroidectomised rats show that thyroxine alone does not ensure euthyroidism in all tissues but that combination T3/T4 therapy does. (31,32) One study using T4 alone on patients with sub clinical hypothyroidism showed decrements in health status, psychological function, working memory, and motor learning.(33)

In humans, T4/T3 treatments reduce serum cholesterol and increase the speed of the Achilles tendon reflexes better than T4 treatments alone, (34) and a goitre can be prevented with T4/T3 combination therapy than with T4 only, even if T4 is given at doses seven times higher than those on T4/T3 treatments. (35)

Prior to the introduction of modern thyroid function testing thyroid hormone titration was based primarily on patient signs and symptoms. The current TSH dominant approach produces lower levels of supplementation and significant morbidity. (36)

Considering the studies' findings related to heart disease, it is interesting to note here that historically, hypercholesterolaemia was one of the clinical signs by which hypothyroidism was diagnosed. There has been no attempt to replicate the original Bunevicius research using adequate doses of thyroid hormone.

A further confounding issue is that this type of research is based on aggregated response. Thyroid hormone levels are not optimised for each patient. For a given titration strategy individual patients may be under or over medicated. Further research is needed on selected patient groups in order to determine the optimum supplementation strategy, according to the cause of hypothyroidism and individual patient response.

Other methodological issues affecting the quality of research are highlighted by Dr Lowe, who notes, in a critique of a paper by Kaplan et al, "as in other studies, (37-45) the thyroid cancer patients undoubtedly improved more because of their higher thyroid hormone dosages. Kaplan et al conjectured however, that thyroid cancer patients improved more, not because of their higher dosages of thyroid hormone - but because they differed in some relevant but undetermined way from autoimmune thyroiditis patients.(46)

There is further research evidence to support the use of T4/T3 combination therapy at the higher dosage levels which suppress the TSH, rather than a supplemental level dose, and in which the study results were not "confounded". (40-44) Other research has shown that patients report feeling better with TSH-suppressive dosages of thyroid hormone. (47-50)

Moreover, psychiatrists report that dosages of T3 higher than at only replacement level augment the depression-relieving effects of antidepressants. (40-45)

One double-blind, randomised, controlled trial studied 141 patients with primary autoimmune hypothyroidism that were randomised to groups treated with T4/T3 in a ratio of either 5:1 or 10:1, and a control group that continued with their previous T4-only treatment. (51) After 15 weeks, the study showed a clear preference by patients for the combination treatments, and in particular, the 5:1 treatment featuring a higher level of T3, versus the T4-only treatment.

In another study in which patients were rendered hypothyroid by therapeutic destruction of the thyroid gland, some participants were given TSH-suppressive dosages of thyroid hormone and others given T4 only replacement. Those on TSH-suppressive dosages did not gain excess weight; those on T4 - replacement did. The researchers concluded that T4-replacement was the cause of the excess weight gain. (52)

Other studies have shown that treatment of obesity using T3 alone with a very low calorie diet helps reduce weight, (53-58) and interestingly, a study published in the European Journal of Endocrinology (Ortega et al 2008) concluded that T3 concentrations might play a role in the regulation of insulin secretion.(59)

Finally, Colin Dayan (Head of Medical Research, University of Bristol) shows that community surveys have repeatedly shown decreased psychological well-being in people on thyroxine only, although the basis of this remains controversial. Recent studies have highlighted that variation in the activity of cell membrane transporters and deioidinases between tissues means that serum levels of thyroid hormone do not necessarily reflect active levels of thyroid hormone within tissues. Current research is using genetic variation to determine the effect of differences in deiodinase activity between individuals on requirements for thyroid hormone. This may also prompt a re-evaluation of the role of combined T4 and T3 replacement in selected individuals. Thyroid hormone replacement.(60)

References:

1. *Willard Owen Thompson, Lawrence L. McLellan, Phebe K. Thompson, and Lois F. N. Dickie "The rates of utilization of thyroxine and of desiccated thyroid in man: The relation between the iodine in desiccated thyroid and in thyroxine". Department of Medicine, Rush Medical College, and The Presbyterian Hospital, Chicago: J Clin Invest. 1933 January; 12(1): 235–246.*
2. *LeBoff, M.S., Kaplan, M.M., Silva, J.E., et al.: Bioavailability of thyroid hormones from oral replacement preparations. Metabolism, 31(9):900-905, 1982.*
3. *Lavietes, P.H. and Epstein, F.H.: Thyroid therapy of myxoedema: A comparison of various agents with a note on the composition of thyroid secretion in man. Ann. Intern. Med., 60:79-87, 1964.*
4. *Gorowski, T., Pucilowska, J., and Wernic, K.: Comparative effects of desiccated thyroid gland and sodium salt of L-thyroxine in the treatment of hypothyroidism. Pol. Tyg. Lek., 44(32-33):768-770, 1989.*
5. *Krenning, E.P., Docter, R., Visser, T.J., et al.: Replacement therapy with L-thyroxine: serum thyroid hormone and thyrotropin levels in hypothyroid patients changing from desiccated thyroid to pure thyroxine substitution therapy. Neth. J. Med., 28(1):1-5, 1981.*
6. *Felt, V. and Nedvidkova, J.: Comparison of treatment with L-thyroxine and a dried thyroid gland preparation in patients with hypothyroidism. Vnitr. Lek., 28 (11):1067-1073, 1982.*
7. *Cobb, W.E. and Jackson, I.M.: Drug therapy reviews: management of hypothyroidism. Am. J. Hosp. Pharm.,35(1):51-58, 1978.*
8. *Wartofsky, L.: Combined levotriiodothyronine and levothyroxine therapy for hypothyroidism: are we a step closer to the magic formula? Thyroid, 14(4):247- 248, 2004.*
9. *Rodriguez, T., Lavis, V.R., Meininger, J.C., et al.: Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr. Pract., 11:223–233, 2005.*
10. *Kosowicz, J., Horst-Sikorska, W., Lacka, K., et al.: Outcome of treating hypothyroidism with thyreoideum. Pol. Tyg. Lek, 48(27-28):599-602, 1993. 38. Warszawie, C.M.K.P.: Treatment of hypothyroidism with L-thyroxine. Pol. Tyg. Lek, 48(27-28):605-608, 1993.*
11. *Singh, S.P., Feldman, E.B., and Carter, A.C.: Desiccated thyroid and levothyroxine in hypothyroidism: comparison in replacement therapy. N.Y. State J. Med., 72(9):1045-1048, 1972.*
12. *Sawin, C.T., Hershman, J.M., Fernandez-Garcia, R., et al.: A comparison of thyroxine and desiccated thyroid in patients*

with primary hypothyroidism. Metabolism, 27(10):1518-1525, 1978

13. *Smith, R.N., Taylor, S.A., and Massey, J.C.: Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. Brit. Med. J., 4:145-148, 1970.*
14. *McGavack, T.H. and Reckendorf, H.K.: Therapeutic activity of desiccated thyroid substance, sodium Lthyroxine and D, L-triiodothyronine: a comparative study. Am. J. Med., 20:774-777, 1956.*
15. *Medicines and Healthcare products Regulatory Agency. Public Assessment Reports.http://www.mhra.gov.uk/Publications/PublicAssessmentReports/CON2032968*
16. *Dr. E. Chester Ridgway, Director of Endocrinology at the University of Colorado Health Sciences Center, Equivalence of Levothyroxine Sodium Products, Joint Public Meeting (Cosponsored with the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists) Monday, May 23, 2005, pages 144-145.*
17. *Medicines and Healthcare Products Regulatory Agency. Yellow Card. http://www.mhra.gov.uk/home/groups/public/documents/sentineldocuments/dap_1235563227759.pdf*
18. *"The treatment of clinically hypothyroid, but biochemically euthyroid patients". The International Hormone Society. Consensus No.1, Septe mber 2005.*
19. *"The application of hormone therapy by multiple medical specialties," The International Hormone Society. Consensus No.1, September 2005.*
20. *Patients' Petition for Better Diagnosis and Treatment Choice for Hypothyroid Patients," International Hormone Society http://intlhormonesociety.org/index.php?option=com_content&task=view&id=31&Itemid=53&tomHack_idp=10*
21. *Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BGA, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ. "Combined thyroxine/liothyromine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism." J Clin Endocrinol Metab 88:4543–4550, 2003.*
22. *Sawka A. M., Gerstein H.C., Marriott M.J., MacQueen G.M., Joffe R.T. "Does a combination regimen of thyroxine (T4) and 3, 5, 3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial." J Clin Endocrinol Metab 88:4551–4555, 2003.*
23. *Clyde, P.W., Harari, A.E., Getka, E.J., and Shakir, K.M.M. "Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial." JAMA, 2003, 290:2952-2958.*
24. *Cassio, A., Cacciari, E., Cicgnani, A., et al. "Treatment of congenital hypothyroidism: thyroxine alone or thyroxine plus triiodothyronine?" Pediatrics, 2003,111(5):1055-1060*
25. *Bunevicius R., Kazanavicius G., Zalinkevicius R., Prange A.J. Jr., Institute of Endocrinology, Kaunas Medical University, Lithuania. "Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism" N Engl.J Med.Feb 11 1999;340424-9*
26. *Bunevicius R., Jakubonien N., Jurkevicius R., Cernicat J., Lasas L., Prange A.J., Institute o Endocrinology, Clinic of the Kaunas Medical University, Lithuania. "Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease." Endocrine, July 18 2002; (2):129-33.*
27. *Opstad P.K., Falch D., Öktedalen O., Fonnum F., and Wergeland R. "The thyroid function in young men during prolonged physical exercise and the effect of energy and sleep deprivation." Clin Endocrinol, 1984; 20: 657-69.*
28. *Bunevicius R., Karanavicius G., Zalinkevicius R., Prange A.J. "Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism." N Engl J Med, 1999; 340: 424 –429*
29. *Asper S.P. Jr, Selenkow H.A., and Plamondon C.A. "A comparison of the metabolic activities of 3, 5, 3'-triiodothyronine and L-thyroxine in myxedema." Bull John Hopkins Hosp, 1953; 93:*
30. *Blackburn C.M., McConahey W.M., Keating F.R. Jr, Albert A. "Calorigenic effects of single intravenous doses of l-triiodothyronine and L-thyroxine in myxedematous persons." J ClinInvest, June 1954; 33(6):819-24 treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat." Endocrinology, June 1996; 137(6): 2490-502.*
31. *Escobar-Morreale H.F., del Rey F.E., Obregon M.J., de Escobar G.M. "Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat." Endocrinology, June 1996; 137(6): 2490-502.*
32. *Escobar-Morreale H.F., Obregon M.J., Escobar del Rey F, Morreale de Escobar G. "Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats." J Clin Invest, December 1995; 96(6):2838.*
33. *Samuels M.H., Schuff K.G., Carlson N.E., Carello P., Janowsky J.S. Division of Endocrinology Diabetes, Oregon Health and Science Univeresity, Portland,Oregon, 97239, USA*
34. *Alley RA, Danowski TS, Robbins T JL, Weir TF, Sabeh G, and Moses CL. Indices during administration of T4 and T3 to euthyroid adults. Metabolism. 1968;17(2):97-104*
35. *Devlin WF, Watanabe H. Thyroxin-triiodothyronine concentrations in thryoid powders. J Pharm Sci. 1966 Apr;55(4):390-3*
36. *Olukoga A.O., Crowley V.E., Lawal A., Weinkove C"Hyperlipidaemia and hypothyroidism." BMJ. Feb 26, 1994; 308(6928):588.*
37. *Carr, C., McLeod, D.T., Parry, G., et al. "Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment." Clin. Endocrinol., 28:325-333, 1988.*
38. *Schlote, B., Schaaf, L., Schmidt, R., et al. "Mental and physical state in subclinical hyperthyroidism: investigation in a normal working population." Biol. Psychiatry, 32(1):48-56, 1992.*
39. *Schlote, B., Nowotny, B., Schaaf, L., et al. "Subclinical hyperthyroidism: physical and mental state of patients." Eur. Arch.*

Psychiatry Clin. Neurosci., 241(6):357-364, 1992.

40. *Wilson, I.C., Prange, A.J. Jr., and Lara, P.P. "L-triiodothyronine alone and with impramine inthe treatment of depressed women." In The Thyroid Axis, Drugs, and Behavior. Edited by A.J. Prange. New York, Raven Press, 1974, pp.49-62.*
41. *Cook R.G Joffe R.T.and Levitt,A.J. T3 Augmentation of anti-depressant treatmentin T4 replaced thyroid patients"J Clin.Psychiatry,1992,53(1):16-18*
42. *Joffe, R.T. and Singer, W. "A comparison of triidothyronine and thyroxine in the potentiation of tricyclic antidepressants." Psychiatry Res., 1990, 32:241-251.*
43. *Altshuler, L.L., Bauer, M., Frye, M.A., et al. "Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature." Am. J. Psychiatry, 2001; 158:1617-1622.*
44. *Stern, R.A., Nevels, C.T., Shelhorse M.E et al."Antidepressants and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: preliminary findings." Biol. Psychiatry, 1991, 30:623-627*
45. *Kaplan, M.M., Sarne, D.H., and Schneider, A.B. "Editorial: In search of the imposs iThyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients." Clin. Endocrinol. Metab., 2003, 88(10):4540-4542*
46. *Lowe, J.C., Reichman, A., Yellin, J. "A case-control study of metabolic therapy for fibromyalgia: long-term follow-up comparison of treated and untreated patients" (abstract). Clin. Bull. Myofascial Ther., 1998, 3(1):23-24.*
47. *Carr, C., McLeod, D.T., Parry, G., et al. "Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin asswith measurement of free thyroid hormones and clinical assessment." Clin. Endocrinol., 128:325-333.*
48. *Schlote, B., Schaaf, L., Schmidt, R., et al. "Mental and physical state in subclinical hyperthyroidism: investigation in a normal working population." Biol. Psychiatry, 1992, 32(1):48-56. 41.*
49. *Schlote, B., Nowotny, B., Schaaf, L., et al. "Subclinical hyperthyroidism: physical and mentastate of patients." Eur. Arch. Psychiatry Clin. Neurosci., 1992, 241(6):357-364*
50. *Appelhof B.C., et. al. "Combined therapy with levothyroxine and liothyronine in two raticompared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial." J Clin Endocrinol Metab., May 2005; 90(5):2666.*
51. *Moore R., Grant A.M., Howard A.N., Mills I.H. "Treatment of obesity obesity with triiodothyronine and a very low-calorie liquid formula diet." Lancet, Feb 2, 1980; 1(8162):223-6.*
52. *Gelvin E.P., Kenigsberg S., Boyd L.J. "Results of addition of liothyronine to a weight-reducing regimen "J Am Med Assoc. Jul 25. 1959;170 (13):1507-12*
53. *Rozen R., Abraham G., Falcou R., Apfelbaum M. "Effects of a 'physiological' dose of triiodothyronine on obese subjects during a protein-sparing diet." Int J Obes, 1986; 10 (4):303-12.*
54. *Pasquali R., Baraldi G., Biso P., Piazzi S., Patrano D.Capelli M., Melchionda N. Effect of 'physiological' doses of triiodothyronine replacement on the hormonal and metabolic adaptation to short-term semistarvation and to low-calorie diet in obese patients." Clin Endocrinol (Oxf), Oct.21, 1984;357-67*
55. *Koppeschaar H.P., Meinders A.E., Schwarz F. "Metabolic responses in grossly obese subjectreated with a very-low-calorie diet with and without triiodothyronine treatment." Int J Obes, 1983; 7(2): 133-41.*
56. *Koppeschaar H.P., Meinders A.E., Schwarz F. "The effect of a low-calorie diet alone and in combination with triiodothyronine therapy on weight loss and hypophyseal thyroid function in obesity." Int J Obes, 1983; 7(2):123-3.*
57. *Wilson J.H., Lamberts S.W. "The effect of triiodothyronine on weight loss and nitrogen balance of obese patients on a very-low-calorie liquid-formula diet." Int J Obes, 1981; 5(3):279-82*
58. *Moore R., Mehrishi J.N., Verdoorn C., Mills I.H. "The role of T3 and its receptor in efficient. Int J Obes., 1981.*
59. *Ortega E., Koska J., Pannacciulli N., Bunt J.C., Krakoff J. "Free triiodothyronine plasma concentrations are positively associated with inEuropean Journal of Endocrinology, 2008, Vol 158, Issue 2, 217-221.*
60. *Colin Dayan.University of Bristol, UK:* Endocrine Abstracts *(2009)* ***19*** *S67* *http://www.endocrine-abstracts.org/ea/0019/ea0019s67.htm*

Part 2 (Armour Thyroid, USP)

> *The RCP state: "We do not recommend the prescribing of …Armour thyroid, as it is inconsistent with normal physiology, has not been scientifically proven to be of any benefit to patients, and may be harmful."*

This statement is ridiculous. TPA-UK cited 148 references to the studies and research in support of their response to the BTA statement on the use of natural desiccated thyroid extract (Armour Thyroid, USP). Many statements by the BTA are misleading, and others are wrong. A rebuttal was sent to the BTA in March 2008. It is of great concern that the BTA never acknowledge receipt of these rebuttals, nor have they amended their incorrect statements. This is grossly irresponsible.

We also disagree with many of the statements made by the RCP on Armour. TPA-UK are concerned that the RCP advise that T4 replacement remains the treatment of choice despite the overwhelming evidence contrary to their opinion, showing T4 alone to be ineffective in relieving many patients' symptoms.(1)

Conventional medical practitioners have made no attempt to evaluate the evidence regarding the use of natural thyroid hormone, and their wholesale dismissal of the concept represents, at least in part, a biased attitude.

Perhaps the greatest advantage of the thyroid therapy with desiccated thyroid was a study by Dr. Broda Barnes on the prevalence of heart attacks in comparison with the famed Framingham study, which showed a substantially lower rate of heart attacks with a desiccated thyroid therapy. (2) And if the subjects dropped out of the desiccated thyroid study, their heart attack rate rapidly reflected the rates of the Framingham study. Danzi and Klein not only verify the cellular need for T3, but also discuss the beneficial regulation of cardiac genes and vasculature. (4)

However and unfortunately, the Barnes study, like so many others done in earlier medicine, has been dismissed unfairly as 'unscientific' because they were not randomised, double-blind and placebo corrected. However, Benson and Hartz found that the results of the properly executed so-called 'unscientific' methods truly reflected good science. (5)

Thyroid extracts continued their popularity and were not affected by the introduction of synthetic thyroxine in the 1930s until a hoax batch of thyroid extract, containing only iodine with no thyroid hormone, was shipped to Europe and the US in 1963, with the goal of discouraging the use of thyroid extracts. This hoax made thyroxine the only eligible thyroid preparation for hypothyroidism because the homophobic domino effect of the 1948 Wolff-Chaikoff publication prevented physicians from supplementing their patients with iodine. (6)

Many doctors were reluctant to switch to thyroxine only, preferring to prescribe the desiccated gland. They were, however, eventually persuaded to change their allegiance.

In 1969, Dr. Wolff from the National Institute of Health published his paper titled, "Iodide goiter and the pharmacologic effects of excess iodide". (6,7)

In 1970, Goodman and Gilman stated,

> *''This episode gave thyroid a bad name because several publications about the unreliability of thyroid appeared before the hoax was uncovered .* (8)

There was widespread concern that the effects of this "drug" were not consistent with previous clinical experience and so all thyroid extract was labelled "unreliable". Although the hoax was uncovered seven years later and 'The Medical Letter' in 1973 maintained that desiccated thyroid extract had never been unreliable, mud sticks, and doctors started using synthetic l-thyroxine.(7)

To quote Derry:

> *". . . by 1976 about half (52%) of the prescriptions written for thyroid hormone in the United States were for desiccated thyroid or other natural products.*(9)

The best pharmacological authorities confirmed desiccated thyroid remains a remarkably, clinically predictable, safe and effective preparation which is well absorbed". So why the continued misinformation perpetrated by the RCP?

All thyroid hormone products, both animal-derived and synthetic, are unstable compared to many other drugs. Thyroid hormones consist of iodine atoms bound to the amino acid tyrosine. The iodine atoms easily separate from the tyrosine". (10)

Therefore, it is prudent for both doctors and patients to be vigilant for sub-potent tablets or capsules.

It appears that some NHS doctors do not recommend Armour thyroid because they believe the amount of thyroid hormone varies between batches and/or they believe the higher ratio of T3 to T4 in Armour could be harmful or cause adverse reactions. The evidence does not support such reasoning, and in fact the variation of thyroid hormone in Armour is minimal and well controlled (maximum 5-10 %) as specified by the US FDA. (11,12)

There are many thyroid extract preparations and the trademark Armour Thyroid should not be used as a generic name for these. There is much evidence that Armour Thyroid is the most reliable of the desiccated thyroid preparations in the US. (12,13-16)

Evidence is presented in the empirical use of Armour thyroid by Gaby that many people have hypothyroidism undetected by laboratory thyroid-function tests, and cases are reported to support the empirical use of Armour Thyroid. Clinical evaluation can identify individuals with sub-clinical hypothyroidism that is likely to benefit from thyroid-replacement therapy. In a significant proportion of cases, treatment with thyroid hormone has resulted in marked improvement in chronic symptoms that had failed to respond to a wide array of conventional and alternative treatments. In some cases, treatment with desiccated thyroid has produced better clinical results than levothyroxine. Research supporting the existence of sub-clinical hypothyroidism is reviewed, and the author's clinical approach to the diagnosis and treatment of this condition is described. (15)

Armour Thyroid does have a higher amount of T3 compared to T4 than the relative amounts of T3 to T4 secreted by the human thyroid gland. However, it is well documented that Armour is often more effective and is better tolerated than synthetic preparations of T4, T3 and T4/T3 combination. (17) This is because the T3 in natural thyroid extract is absorbed more slowly than synthetic (purified, unbound) T3. (18)

The normal thyroid gland contains approximately 200 mcg of T4 per gram of gland, and 15 mcgs of T3 per gram. The ratio of these two hormones in the circulation does not represent the ratio of the thyroid gland, since about 80% of peripheral T3 comes from monodeiodination of T4. Peripheral monodeiodination of T4 also results in the formation of reverse T3, which is inactive. (19)

A similar ratio can be obtained by prescribing both Armour and synthetic thyroxine, although clinical response and symptom control should take precedence over a theoretical ideal. Perhaps the ultimate form of thyroxine for difficult patients is whole thyroid extracted from animals, such as Armour thyroid tablets. (20-22)

The long history of successful use thyroid extract in America has seen natural thyroid extract products successfully compete with the heavily promoted synthetic T4 and T3 preparations. Not only are whole glandular extracts often superior to T4 for the treatment of hypothyroidism, but there is evidence to suggest that such products are also superior to combined synthetic T4/T3 preparations.(23,24)

Shames and Shames report a patient who was treated unsuccessfully with a combination of T4 and T3 who experienced a dramatic improvement when switched to Armour thyroid extract. (24) When synthetic T4 and T3 first became available, Arem reports the considerable difficulties he experienced when switching patients from thyroid extracts to the new synthetic preparations. (23)

According to Arem:

> *"The new treatment was seldom entirely successful."* Arem continues*: "Once switched from these natural T4/T3 tablets to T4 tablets, patients complained of sluggishness, decreased memory, impaired concentration, and a host of symptoms of ill-being. This was in spite of having reached normal blood levels of thyroid hormone and TSH."*

Since at least a third of treated hypothyroid patients whose blood tests have been restored to "normal" continue to have symptoms, therefore modern thyroid treatment is often unsuccessful, a fact which is hardly surprising given the fact that T3 is the crucially important active thyroid hormone; and the

commonly seen failure to convert T4 to T3 (and also, to a lesser extent T2) will result in an unsatisfactory treatment outcome. (23-26)

This underlines the urgent need to rethink methods of thyroid treatment. Clearly, much greater priority must be given to a symptomatic approach and the importance of how the patient feels, given the overwhelming evidence of the relative ineffectiveness of T4 and the dubious usefulness of the serum TSH test alone for diagnosis. Over reliance on laboratory tests, without clinical evaluation, may lead to considerable diagnostic errors. (27-30)

Hypothyroid patients who remained polysymptomatic on T4 treatment who were switched to Armour thyroid extract became biochemically euthyroid and completely symptom-free. (31)

Many millions of patients throughout the world have used and continue to use natural thyroid extract. Before the advent of the TSH test in the early 1970s, patients used these products in much higher dosages than nowadays. (32)

There may be advantages to using Armour that are not related to its T3 content. Broda Barnes observed some patients treated with syntheticT4/T3 combination continued to experience residual symptoms, particularly dry skin and oedema. Both symptoms resolved in 1-2 months when the treatment was changed to Armour. (33)

This observation suggests a third active substance is secreted by the thyroid gland. The most likely candidate is 3, 5-diiodo-l-thyronine (T2). Although little was known about the function of this compound in humans, the widely held assumption that it is metabolically inert may be incorrect. The fact is T2 is indeed very active in terms of metabolic effects.

The manufacturers of Armour Thyroid to USP (Forest Pharmaceuticals) have done no studies into the specific amount of the other thyroid hormones in Armour, T2, T1, calcitonin or any other 'T' hormones that are naturally occurring in the desiccated thyroid. Nothing has been removed in the processing and many endocrinologists believe there is little (or no) information about T2 or monoiodothyronine (T1). However, this is not the case.

The use of T2 has been shown to increase hepatic oxygen consumption by about 30%. The authors of one study discovered only T2 was active in stimulating rapid hepatic oxygen consumption. They concluded that it acts rapidly and directly through activation of the mitochondria. (34)

In another study, T3 and T2 were compared in terms of Resting Metabolism (RM) and on the oxidative capacity of tissues that are metabolically active (liver, muscle tissue, brown adipose tissue or BAT, and heart). What they found was that T2 had a dose-dependent effect which increased RM and oxidative capacity. They found the greatest response to T2 was in the liver and in BAT. The effects again, occurred rapidly and independent of protein synthesis. They stated that their results suggested isomers like T2 could be direct mediators of thyroid hormone regulation on energy metabolism. (35, 36)

Yet another study also found increased hepatic oxidative capacity and thought that it was due to a direct action upon the mitochondria by T2. (37) Other studies had similar findings. (38,39) Another study showed the same thing: increased oxidative capacity and energy expenditure, causing them to deduce that T2 and T3 displayed similar effects. (40) T2 was also shown to have a similar effect to that of T3 on lipid metabolism with T2 actually doing a little better in some tissue. (41)

Although there isn't a *huge* amount of research in humans, some does exist. In one study, using human mononuclear blood cells, they found that T2 increased the rate of respiration significantly. (42) So, the efficacy appears to have been established. Can it significantly inhibit TSH like T3 and T4? Well, the studies are somewhat conflicting, but one thing seems to be prevalent amongst them all. That is, TSH inhibition isn't nearly as severe with T2 as it is with T3. One study showed that T2 is 13% less inhibitory on TSH levels, as compared to T3. (43)

In yet another study, T3 and T2 suppressed TSH to similar levels; however, it took 15 mcg / 100g body weight per day of T3 to accomplish this, while it took 200 mcg/100g body weight per day of T2 to accomplish the same thing. This means it took about 13 times more T2 to exert the same effect on TSH as T3. (44)

When researchers administered 100 ug/kg of T3 and 800-1600 ug/Kg of T2 the following occurred: T3 rapidly decreased serum TSH levels within minimal levels after 24 hours. Seventy-two hours after application, TSH levels were still significantly lower than control levels. As far as the T2, TSH levels were transiently reduced and reached their lowest point at 24 hours and increased afterwards. Basal levels were reached 72 hours after an application.

What they found after analysing the data was that there seemed to be a trend for a dose-dependent suppression of TSH by T2 which did not reach statistical significance. That means it didn't do it to a significant degree with the dosages used.

Furthermore, it appears as though it took 100 times more T2 than T3 to finally exert the same amount of TSH inhibition. Even using 400 times more T2 than T3, it appears that T3 only allows TSH to be inhibited to just a slight degree less than T2.

The RCP statement that "Armour is inconsistent with normal physiology and that it has not been scientifically proven to be of any benefit to patients and may be harmful" is more than nonsensical - it is false. There is, as has been demonstrated in this paper, overwhelming scientific evidence to the contrary.

Armour Thyroid is no more likely to cause side effects than is a synthetic T4/T3 combination. Splitting the daily dose of Armour would obviate any potential concern about transient elevations of T3 levels.(12)

Thyroxine was introduced <u>without any comparison with natural thyroid extract.</u> The Medicines Control Agency (MCA) has continued its use without review. Given that levothyroxine is the cheaper medication, one has to question why the manufacturers would not wish to demonstrate equal effectiveness. Natural thyroid extract has been making patients better since 1894, long before the introduction of synthetic thyroxine. Thus, the burden of proof lies with the synthetic product to demonstrate it is as safe, effective and as consistent as Armour. (12,13)

The MHRA does allow doctors to prescribe Armour Thyroid from Forest Pharmaceutical. (45) They would <u>not</u> allow this if it was "harmful" and neither would the FDA have approved it as a fully official registered drug in the USA.

References:

1. *The Association of Clinical Biochemists, The British Thyroid Association, The British Thyroid Foundation. "UK Guidelines for the Use of Thyroid Function Tests". July 2006. http://www.acb.org.uk/docs/TFTguidelinefinal.pdf*
2. *Barnes, B MD, Hypothyroidism: The Unsuspected Illness, Harper & Row, 1976, pgs 142-144, 178-181*
3. *Willard Owen Thompson, Lawrence L. McLellan, Phebe K. Thompson, and Lois F. N. Dickie "THE RATES OF UTILIZATION OF THYROXINE AND OF DESICCATED THYROID IN MAN: THE RELATION BETWEEN THE IODINE IN DESICCATED THYROID AND IN THYROXINE". Department of Medicine, Rush Medical College, and The Presbyterian Hospital, Chicago: J Clin Invest. 1933 January; 12(1): 235–246.*
4. *Danzi S, Ojamaa K, and Klein I, Triiodothyronine-Mediated Myosin Heavy Chain Gene Transcription in the Heart, Am J Phys Heart Circ Physiol, Feb 27, 200*
5. *Benson K, Hartz AJ, A Comparison of Observation Studies and Randomized Controlled Trials, NEJM, June 22, 2000, pgs 1878-86.*
6. *Abraham GE. "The Wolff-Chaikoff effect: Crying wolf?" The Original Internist, 2005; 12(3):112-118.*
7. *Abraham GE. "The History of Iodine in Medicine Part lll: Thyroid Fixation and Medical Iodophobia" June 2006. The Original Internist, 13:71-78*
8. *Astwood EB et al. Goodman and Gilman's the Pharmacological Basis of Therapeutics, fourth ed. New York: The Macmillan Company; 1970.*
9. *Derry DM. Breast Cancer and Iodine. Trafford Publ., Canada, 2001; 39.*

10. *Abraham GE. "The safe and effective implementation of orthoiodo supplementation in medical practice." The Original Internist, 2004; 11(1):17-36.*
11. *Lowe, John. "Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients." May 4, 2004 http://www.drlowe.com/frf/t4replacement/intro.htm*
12. *Steven L. Richheimer, Charlotte B. Jensen. Response to "Liothyronine and Levothyroxine in Armour Thyroid?": 1987.Journal of Pharmaceutical Sciences. Volume 76, Issue 4. Pages 346-347*
13. *Rees-Jones RW, Larsen PR. Triiodothyronine and thyroxine content of desiccated thyroid tablets". Metabolism. 1977 Nov;26(11):1213-8*
14. *Rees-Jones RW, Rolla AR, Larsen PR. "Hormonal content of thyroid replacement preparations". JAMA. 1980 Feb 8;243(6):549-50.*
15. *LeBoff MS, Kaplan MM, Silva JE, Larsen PR. "Bioavailability of thyroid hormones from oral replacement preparations". Metabolism. 1982 Sep;31(9):900-5.*
16. *Gaby AR."Sub-laboratory hypothyroidism and the empirical use of Armour thyroid". Altern Med Rev. 2004 Jun;9(2):157-79*
17. *Hertoghe T, Lo Cascio A., Hertoghe J. "Considerable improvement of hypothyroid symptoms with two combined T3-T4 medication in patients still symptomatic with thyroxine treatment alone". Anti-Aging Medicine (Ed. German Society of Anti-Aging Medicine-Verlag 2003) 2004; 32-43*
18. *Alan R. Gaby, MD "Alternative Medicine Review" Volume 9, Number 2, 2004*
19. *Armour Thyroid (thyroid tablets USP). http://www.frx.com/pi/armourthyroid_pi.pdf*
20. *Mary Shomon: "Armour Thyroid and Thyrolar; Alternatives to Synthroid and the Other TG4 Only Drugs. December 26th. 2003. About.com/Thyroid. http://thyroid.about.com/library/weekly/aa111797.htm*
21. *Gail Valentine. "The Advantages of whole thyroid; Slowing Age-related Decline, Life Enhancement. http://www.life-enhancement.com/displayart.asp?ID=232*
22. *Arem, R., The Thyroid Solution, Ballantine Books, 1999, New York.*
23. *Shames, RL, Shames, KH, Thyroid Power: 10 Steps to Total Health, Harper Collins Publishers, New York, 2001.*
24. *Saravanan, P., et al, Clinical Endocrinology 57 (5), 577-585, 2002.*
25. *Rothfeld, G.S., Romaine, D.S., "Thyroid Balance: Traditional and Alternative Methods for Treating Thyroid Disorders", Adams Media Corporation, Avon, Massachusetts, USA, 2003.*
26. *Nicoloff JT, Spencer CA. "The use and misuse of the sensitive thyrotropin assay". J Clin Endocrinol Metab. 1990;71:553-8.*
27. *De Los Santos ET, Mazzaferri EL. "Sensitive thyroid-stimulating hormone assays": Clinical applications and limitations. Compr Ther. 1988; 14(9): 26-33.*
28. *Becker DV, Bigos ST, Gaitan E, Morris JCrd, Rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. "Optimal use of blood tests for assessment of thyroid function". JAMA 1993 Jun 2; 269: 273 ("the decision to initiate therapy should be based on both clinical and laboratory findings and not solely on the results of a single laboratory test")*
29. *Rippere V. Biochemical victims: "False negative diagnosis through overreliance on laboratory results—a personal report". Med Hypotheses. 1983; 10(2): 113*
30. *Gautam Das, Shweta Anand & Parijat De. Diabetes & Endocrine Unit, City Hospital, Birmingham, United Kingdom Endocrine Abstracts (2007)13 P316*
31. *Pearch, C.J. and Himsworth, R.L. "Total and free thyroid hormone concentration in patients receiving maintenance replacement treatment with thyroxine". Brit. Med. J., 288: 693-695, 1984.*
32. *Barnes BO. "Is there a third hormone in the thyroid gland? Which preparation should be used for treatment?" J Int Acad Prev Med 1982; November:38-39.*
33. *Horst C, et al. "Rapid stimulation of hepatic oxygen consumption by 3,5-di-iodo-L-thyronine." Biochem J 1989 Aug 1;261(3):945-50*
34. *Lanni A, et al. "Calorigenic effect of diiodothyronines in the rat." J Physiol 1996 Aug 1;494 (Pt 3):831-7*
35. *Goglia F, et al. "Action of thyroid hormones at the cellular level: the mitochondrial target." FEBS Lett 1999 Jun 11;452(3):115-20*
36. *Lanni A, et al. "Effect of 3,3'-diiodothyronine and 3,5-diiodothyronine on rat liver oxidative capacity." Molecular and Cellular Endocrinology. Volume 86, Issue 3. 1992*
37. *Lanni A, et al. J. Endocrinol. 136:59-64 1993.*
38. *O'Reilly I, Murphy MP. Acta Endocrinol. 127:542-546 1992.*
39. *Lanni A, et al. "3,5-Diiodo-L-thyronine and 3,5,3'-triiodo-L-thyronine both improve the cold tolerance of hypothyroid rats, but possibly via different mechanisms." Pflugers Arch 1998 Aug;436(3):407-14*
40. *Varghese S, Oommen OV. "Thyroid hormones regulate lipid metabolism in a teleost Anabas testudineus (Bloch)." Comp Biochem Physiol B Biochem Mol Biol 1999 Dec;124(4):445-5*
41. *J. Kvetny. Horm. Metab. Res. 24:322-325, 1992.*
42. *Moreno M, et al. "Effect of 3,5-Diiodo-L-thyronine on thyroid stimulating hormone and growth hormone serum levels in hypothyroid rats." Life Sciences, Volume 62, No.26, pp. 2369-2377, 1998.*
43. *Horst C, et al. "3,5-Di-iodo-L-thyronine suppresses TSH in rats in vivo and in rat pituitary fragments in vitro." J Endocrinol 1995 May;145(2):291-7*
44. *Baur A, et al. "3,5-diiodo-L-thyronine stimulates type 1 5' deiodinase activity in rat anterior pituitaries in vivo and in reaggregate cultures and GH3 cells in vitro." Endocrinology 1997 Aug;138(8):3242-8.*
45. *Matthews,G. "Armour Thyroid and Porcine Thyroid Extract Replacement Therapy". . June 29.2004.Medicines and Healthcare Products Regulatory Agency MHRA letter*

Huge cost to the NHS of Improper Treatments

A further, and very important consideration to be taken into account, is the considerable cost to the NHS of other medicines prescribed for sufferers of the symptoms of hypothyroidism and its mimics. Hypothyroid patients chronically used more prescription drugs, especially for diabetes, cardiovascular disease and gastrointestinal conditions. (1) These are a great financial burden to the NHS and an overwhelming burden to the quality of life of the tens of thousands of hypothyroid sufferers in the UK alone.

Irving Kirsch's recent Department of Psychology at the University of Hull study (25 February 2008) is the first to examine both published and unpublished evidence of the effectiveness of selective serotonin re-uptake inhibitors (SSRIs), which account for 16 million NHS prescriptions a year. The largest study of its kind concluded that antidepressant drugs DO NOT WORK. More than £291 million was spent on antidepressants in 2006, including nearly £120 million on SSRI. (2)

Depression has an association with lower thyroid hormone levels (3-13) and research has shown that improvement can be achieved with thyroid hormone replacement. (14-21)

There is also an association with anxiety and lower thyroid hormone levels (22-27) and yet again, research has shown improvement with thyroid treatment replacement therapy. (28,29)

Memory loss and Alzheimer's disease likewise have an association with lower thyroid hormone levels. (30,31-34) Both these conditions have shown improvement with thyroid treatment.(35-38)

References:

1. *Lowe, John. "Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients." May 4, 2004 http://www.drlowe.com/frf/t4replacement/intro.htm*
2. *Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, et al. "Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration." 2008, PLoS Med 5(2): e45 doi:10.1371/journal.pmed.0050045: Access full article at http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050045*
3. *Pop VJ, Maartens LH, Leusink G, van Son MJ, Knottnerus AA, Ward AM, Metcalfe R, Weetman AP. "Are autoimmune thyroid dysfunction and depression related? " J Clin Endocrinol Metab. 1998 Sep;83(9):3194-7*
4. *Haggerty JJ Jr, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ Jr. "Subclinical hypothyroidism: a modifiable risk factor for depression? " Am J Psychiatry. 1993 Mar;150(3):508-10*
5. *Gold MS, Pottash AL, Extein I. "Symptomless autoimmune thyroiditis in depression." Psychiatry Res. 1982 Jun;6(3):261-9*
6. *O'Shanick GJ, Ellinwood EH Jr. "Persistent elevation of thyroid-stimulating hormone in women with bipolar affective disorder. " Am J Psychiatry. 1982 Apr;139(4):513-4*
7. *Howland RH. "Thyroid dysfunction in refractory depression: implications for pathophysiology and treatment." J Clin Psychiatry. 1993 Feb;54(2):47-54*
8. *Kirkegaard C, Norlem N, Lauridsen UB, Bjorum N, Christiansen C. "Protirelin stimulation test and thyroid function during treatment of depression." Arch Gen Psychiatry. 1975 Sep;32(9):1115-8*
9. *Bauer MS, Whybrow PC, Winokur A. "Rapid cycling bipolar affective disorder. I. Association with grade I hypothyroidism." Arch Gen Psychiatry. 1990 May;47(5):427-32*
10. *Haggerty JJ Jr, Evans DL, Golden RN, Pedersen CA, Simon JS, Nemeroff CB. "The presence of antithyroid antibodies in patients with affective and nonaffective psychiatric disorders." Biol Psychiatry. 1990 Jan 1;27(1):51-60*
11. *Gaby AR."Sub-laboratory hypothyroidism and the empirical use of Armour thyroid". Altern Med Rev. 2004 Jun;9(2):157-79*
12. *Joffe RT, Marriott M. "Thyroid hormone levels and recurrence of major depression." Am J Psychiatry. 2000 Oct;157(10):1689-91 ("the time to recurrence of major depression was inversely related to T3 levels but not to T4 levels")*
13. *Afflelou S, Auriacombe M, Cazenave M, Chartres JP, Tignol J. "Administration of high dose levothyroxine in treatment of rapid cycling bipolar disorders. Review of the literature and initial therapeutic application apropos of 6 cases." Encephale. 1997 May-Jun;23(3):209-17*
14. *Afflelou S, Auriacombe M, Cazenave M, Chartres JP, Tignol J. "Administration of high dose levothyroxine in treatment of rapid cycling bipolar disorders. Review of the literature and initial therapeutic application apropos of 6 cases." Encephale. 1997 May-Jun;23(3):209-17*
15. *Bauer M, Baur H, Berghofer A, Strohle A, Hellweg R, Muller-Oerlinghausen B, Baumgartner A. "Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders." J Affect Disord. 2002 Apr;68(2-3):285-94*

16. *Schwarcz G, Halaris A, Baxter L, Escobar J, Thompson M, Young M. "Normal thyroid function in desipramine nonresponders converted to responders by the addition of L-triiodothyronine." Am J Psychiatry. 1984 Dec;141(12):1614-6*
17. *Prange AJ Jr. "Novel uses of thyroid hormones in patients with affective disorders." Thyroid. 1996 Oct;6(5):537-43*
18. *Birkenhager TK, Vegt M, Nolen WA. "An open study of triiodothyronine augmentation of tricyclic antidepressants in inpatients with refractory depression." Pharmacopsychiatry. 1997 Jan;30(1):23-6*
19. *Joffe RT, Singer W, Levitt AJ, MacDonald C. "A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression." Arch Gen Psychiatry. 1993 May;50(5):387-93*
20. *Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, Leight KL, Whybrow PC. "Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature." Am J Psychiatry. 2001 Oct;158(10):1617-22*
21. *Kikuchi M, Komuro R, Oka H, Kidani T, Hanaoka A, Koshino Y. "Relationship between anxiety and thyroid function in patients with panic disorder." Prog Neuropsychopharmacol Biol Psychiatry. 2005 Jan;29(1):77-81*
22. *Bauer M, Priebe S, Kurten I, Graf KJ, Baumgartner A. "Psychological and endocrine abnormalities in refugees from East Germany: Part I. Prolonged stress, psychopathology, and hypothalamic-pituitary-thyroid axis activity." Psychiatry Res. 1994 Jan;51(1):61-73*
23. *Magliozzi JR, Maddock RJ, Gold AS, Gietzen DW. "Relationships between thyroid indices and symptoms of anxiety in depressed outpatients." Ann Clin Psychiatry. 1993 Jun;5(2):111-6*
24. *Sait Gonen M, Kisakol G, Savas Cilli A, Dikbas O, Gungor K, Inal A, Kaya A. "Assessment of anxiety in subclinical thyroid disorders." Endocr J. 2004 Jun;51(3):311-5*
25. *Larisch R, Kley K, Nikolaus S, Sitte W, Franz M, Hautzel H, Tress W, Muller HW. "Depression and anxiety in different thyroid function states." Horm Metab Res. 2004 Sep;36(9):650-3*
26. *Constant EL, Adam S, Seron X, Bruyer R, Seghers A, Daumerie C. "Anxiety and depression, attention, and executive functions in hypothyroidism." J Int Neuropsychol Soc. 2005 Sep;11(5):535-44*
27. *Landen M, Baghaei F, Rosmond R, Holm G, Bjorntorp P, Eriksson E. "Dyslipidemia and high waist-hip ratio in women with self-reported social anxiety." Psychoneuroendocrinology. 2004 Sep;29(8):1037-46 (Serum levels of free thyroxin (14+/-2 vs. 16+/-4, P=0.04) were lower in subjects confirming social anxiety)*
28. *Venero C, Guadano-Ferraz A, Herrero AI, Nordstrom K, Manzano J, de Escobar GM, Bernal J, Vennstrom B. "Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor," 2005.*
29. *Nakanishi T. "Consideration on serum triiodothyronine (T3), thyroxine (T4) concentration and T3/T4 ratio in the patients of senile dementia - is it possible to prevent cerebro-vascular dementia?" Igaku Kenkyu. 1990 Feb;60(1):18-25*
30. *Molchan SE, Lawlor BA, Hill JL, Mellow AM, Davis CL, Martinez R, Sunderland T. "The TRH stimulation test in Alzheimer's disease and major depression: relationship to clinical and CSF measures." Biol Psychiatry. 1991 Sep 15;30(6):567-76*
31. *Burmeister LA, Ganguli M, Dodge HH, Toczek T, DeKosky ST, Nebes RD. "Hypothyroidism and cognition: preliminary evidence for a specific defect in memory." Thyroid. 2001 Dec;11(12):1177-85*
32. *Monzani F, Pruneti CA, De Negri F, Simoncini M, Neri S, Di Bello V, Baracchini Muratorio G, Baschieri L. "Preclinical hypothyroidism: early involvement of memory function, behavioral responsiveness and myocardial contractility." Minerva Endocrinol. 1991 Jul-Sep;16(3):113-8*
33. *Baldini IM, Vita A, Maura MC, Amodei V, Carrisi M, Bravin S, Cantalamessa L. "Psychopathological and cognitive features in subclinical hypothyroidism." Prog Neuropsychopharmacol Biol Psychiatry. 1997 Aug;21(6):925-35*
34. *Ganguli M, Burmeister LA, Seaberg EC, Belle S, DeKosky ST. "Association between dementia and elevated TSH: a community-based study. " Biol Psychiatry. 1996 Oct 15;40(8):714-25*
35. *Monzon Monguilod MJ, Perez Lopez-Fraile I. "Subclinical hypothyroidism as a cause of reversible cognitive deterioration." Neurologia. 1996 Nov;11(9):353-6*
36. *Kinuya S, Michigishi T, Tonami N, Aburano T, Tsuji S, Hashimoto T. "Reversible cerebral hypoperfusion observed with Tc-99m HMPAO SPECT in reversible dementia caused by hypothyroidism." Clin Nucl Med. 1999 Sep;24(9):666-8*
37. *Monzani F, Del Guerra P, Caraccio N, Pruneti CA, Pucci E, Luisi M, Baschieri L. "Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment." Clin Investig. 1993 May;71(5):367-71*
38. *Medline Plus. The MedMaster™ Patient Drug Information database. "Liothyronine": http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682462.html#side-effects*

CONCLUSIONS

The RCP recommend that patients with suspected primary hypothyroidism should only be diagnosed with blood tests including measurement of TSH.

The RCP conclusions are alarming and certainly most worrying. TPA-UK does not agree with many of the RCP conclusions, in particular, conclusion (d) which boycotts the use of any and all T3 containing hormone replacements, since those replacements are absolutely necessary for mitigating symptoms produced by these peripheral thyroid deficiencies.

The diagnosis of hypothyroidism, since before 1900, was made on clinical grounds. It's not difficult: there are very many symptoms and signs, and great physicians - we think of Eugene Hertoghe and Broda Barnes, and many others - who were perfectly capable of making good and sound clinical diagnosis on the basis of a proper history and examination, and did so from 1900 up to the present day. By the 1960s blood tests for thyroid function became available, but after several years of use, were each in turn consigned to history owing to their unreliability. Eventually the serum free T4, serum free T3, the TSH became widely accepted, but had serious defects. Those used today are held out by the establishment; RCP, BTA, BTF, the Society for Endocrinology etc, to be reliable. The technology of them is certainly better, but the problem now is their interpretation in the light of the clinical findings. So long as you don't listen to the patient, or actually examine them, the tests provide a logical basis for treatment. The trouble is, human beings don't lend themselves to being placed in boxes.

Today, EBM means blood tests; there is no room for the evidence from the patient. Indeed, doctors are now regularly taken to task for practising the old-fashioned art of listening to and examining their patients. Treatment decisions have to be made on blood tests alone as stated in the RCP guidelines, or the doctor's head may roll. It seems impossible to convince doctors following the party line, that the results of tests may not actually reflect what is happening in the body. A simple example is the level of the thyroid hormone thyroxine. The test may show it is normal (although the patient may have a dozen or more symptoms showing that they actually are quite unwell).

Suppose the level is like it is because the patient cannot use the thyroxine properly, convert it and absorb it into the tissues? So it looks all right but only because it's not being used, you may be surprised to hear this is a **very** common scenario, probably, indeed, the usual reason why the diagnosis gets missed. Why this happens relates to complications following adrenal fatigue, systemic illness (notably candidiaisis), and upsets in other hormones (as at the menopause). But the denial by so many doctors, that this happens, borders on the hysterical so anxious are they to find other reasons for the hypothyroid symptoms. The favourite is depression (see above), as many of us well know. But personality disorder, menopause, overwork, relationship difficulties are others. Prof. Weetman's infamous 'functional somatoform disorder' comes in here as well.

Good medicine means that some back up to clinical judgement is used – but not, please, instead of it. Interpretation of tests is often casual and misplaced. The gold standard is the thyroid stimulating hormone, the TSH. If it is low, you have to be perfectly all right; if it's very low, you are hyperthyroid – overactive – or wickedly taking too much thyroxine replacement. Doctors are often faced with low TSH (equals overactive or over-replaced) **and** a **low** thyroxine - meaning you are under-active. Usually they can't work this out, and decide that whatever the thyroxine is, their patient is having too much. It never occurs to some doctors that the pituitary, or hypothalamus, or adrenal glands may be at fault.

An excellent test, notably the 24 hour urinary thyroid hormones (mentioned above), is rubbished by the RCP in the reference to "other body fluids". Excellent papers are available to point out their efficacy, but these continue to be ignored. Analytical and clinical validation has been shown (above) to anyone who will read it, or listen. But, the RCP, BTA et al., refuse to do either. *'We don't do (accept this test); put it away'*. How arrogant. How ignorant. Just because the RCP et al know nothing about this test, doesn't lessen its value. This test is generally to be preferred over standard thyroid function tests because it shows the amount of thyroid being used, not simply how much is there – and perhaps **not** being used….but they don't appear to understand.

> *The RCP recommend that patients with primary hypothyroidism should be treated with T4 using levothyroxine tablets (BNF) alone.*

It is with increasing despondency we come to guideline (b), where doctors are told they should use BNF thyroxine, only, and exclusively. Surely the writers of this statement know that the thyroid produces other hormones beside T4? What about T3, T2, T1, calcitonin?

What's so wrong doing it nature's way? And what happens to the thyroxine? It all changes into T3. All of it, or if in excess, reverse T3. So why is T4 thought to be the only possible treatment? There is NO reason. It is one of those beliefs by doctors ever since thyroxine was first synthesised. And wasn't it an extraordinary thing that the natural thyroid extract, used for more than 50 years as the ONLY treatment, was suddenly the inferior preparation; that the new synthetic thyroxine – without the **other** thyroid hormones - was so much better. And that now, users of natural thyroid extract, after 50 or more years of further use, are told they must prove the older preparation is as good as the newer, synthetic, thyroxine only preparation. Not the other way round.

> *The RCP state that there is no indication for the prescription of T4 or any preparation containing thyroid hormones to patients with thyroid blood tests within the reference ranges.*

….. except that perhaps the tests are wrong, or wrongly interpreted, and that the patient may actually benefit. Why not try it and see. If the clinical acumen of the doctor is such that s/he has the confidence to make a diagnosis, which doesn't happen to agree with the blood test, s/he should still be in a position to treat. It's safe enough. While treating primary hypothyroidism with only levothyroxine sodium (a T4 replacement) alone is reasonable, although debatable, demanding that there is NO indication for the prescription of any thyroid hormones to patients with thyroid blood tests within the reference ranges is improper, because the thyroid blood tests do not test for all malfunctions of the greater thyroid realm, in particular the 'post thyroid' realm.

> *The RCP state that in patients with suspected primary hypothyroidism, there is no indication for the prescription of T4 or any preparation containing thyroid hormones to patients with thyroid blood tests initially within the normal range. Thus patients with normal T4 and TSH do not have primary hypothyroidism and even if they have symptoms which might suggest this, should not be given thyroid hormone replacement therapy.*

What has NOT been said in the RCP statement is that, if the patient survives, other causes of low thyroid function, such as in liver disease, where the patient develops myxoedema, for instance, can be fatal. There is therefore need to treat those with a high normal TSH who have positive TPO antibodies and/or a goitre. Additionally, in those patients with known pituitary problems, central hypothyroidism should be suspected if they have a low free T4 and a low normal or low TSH.

Bottom line: however ill the patient is and however sure you are of the diagnosis - if the tests don't support the diagnosis - don't treat. Conclusion (d) can only be true if there were no mimics to hypothyroidism. However, there <u>are</u> mimics - which have been known for 40 years. Patients with suspected primary hypothyroidism have the same symptoms as patients with the 'post thyroid' mimics of hypothyroidism, consequently, there is the potential need for proper therapy - potentially and probably a T3 therapy. While patients with normal thyroid blood tests may not have primary hypothyroidism or may have a corrected primary hypothyroidism, these tests do <u>not</u> rule out peripheral metabolism, peripheral cellular hormone reception, the action of the nuclei, or the need for a T3 hormone replacement therapy. Quite often, these tests are limited to the product of the pituitary, the TSH. The validity of this test depends upon the proper operation of the pituitary, which is not a component of the investigation for the causes of the symptoms of hypothyroidism.

Hypocrisy

> *The RCP states that the College does not support the use of thyroid extracts or thyroxine and T3 combinations without further validated research published in peer-reviewed journals. Therefore, the inclusion of T3 in the treatment of hypothyroidism should be reserved for use by accredited endocrinologists in individual patients.*

Interestingly, a service of the U.S. National Library of Medicine and the National Institutes of Health shows on the page at the top of the list under 'other papers': Armour Thyroid: It is ALWAYS there for all thyroid papers. What logical reason do the RCP, BTA et al have to dispute the integrity of the NIH in the USA or its National Library of Medicine?

Either Armour retains its former utility and relevance to treatment of hypothyroidism - or it does not. Either a medical practitioner can prescribe T3 (either synthetic or natural) where this is indicated, or he cannot. We suspect a glaringly obvious witch-hunt is being perpetrated against a very few British individuals, which we know is causing consternation and alarm in our colleagues across the Atlantic. Sham peer reviews have been organised against a few US doctors, in a similar vein to that action against a very few doctors in Britain.

Increasingly, dogma is being 'tarted up' to the status of peer reviewed publications in reputable Journals, where the funders of the research have ulterior motives for publication of results that show negative conclusions - where the reverse is usually the case. Negative results are usually hidden.

TPA-UK has demonstrated that there have been pages of papers published about the use of natural thyroid, thyroxine and liothyronine. Don't the doctors read their journals? It's a case of - if you keep saying one thing, as loud and often as you can, then eventually other doctors will be brainwashed into believing it.

Thyroid extracts have been proven over the past century to be safe and effective. The difficulty with an old therapy is that it was developed prior to the requirement for expensive, randomised, placebo corrected, double-blind clinical testing. However, a study comparing the results of good old science with modern expensive science found that the results were quite comparable.

Quite simply, no matter what the RCP, BTA state, they have yet to produce evidence thatT4 - only monotherapy fully resolves every patient's symptoms.

> *The RCP state that, laboratories which measure thyroid function in other bodily fluids besides blood need to provide analytical and clinical validation to demonstrate their efficacy.*

The RCP need to provide analytical and clinical validation to demonstrate the efficacy of their guideline on the diagnosis and treatment of primary hypothyroidism. Old testing measures have been improperly dismissed. This statement has been dealt with above.

> *The RCP state: "The above statements reflect best practice of clinical endocrinologists accredited by the Royal College of Physicians and the Royal College of Paediatrics and Child Health."*

Such a statement is OPINION ONLY. The papers and journals are there to be read, anything new which shows commonsense should be taken on board as a matter of course. Not doing so places the RCP's. "best practice" in a completely jaundiced light.

Only one conclusion can be arrived at – once this statement goes beyond the scope of 'primary hypothyroidism' and trespasses upon exo-endocrine functions, symptoms, and therapies, it completely contradicts medical science. The problem then becomes this question, "…what human frailties created a contradiction with well-known and established medical science?" Indeed, what has caused the failure to recognise the failure of the levothyroxine sodium only therapy for the past half century?

CONCERNS ABOUT THE RECENT 'JOINT STATEMENT' BY THE ROYAL COLLEGE OF PHYSICIANS ET AL IN RELATION TO 'THE DIAGNOSIS AND MANAGEMENT OF PRIMARY HYPOTHYROIDISM'

Please see below the concerns about the 'joint statement' entitled, 'The Diagnosis and Management of Primary Hypothyroidism' recently made on behalf of the Royal College of Physicians, (in particular its Patient and Carer Network and the Joint Speciality Committee for Endocrinology & Diabetes), The Association for Clinical Biochemistry, The Society for Endocrinology, The British Thyroid Association, The British Thyroid Foundation Patient Support Group, The British Society of Paediatric Endocrinology and Diabetes. This statement, which was also endorsed by The Royal College of General Practitioners, was recently published as an article in the BTF News magazine [1] and as a link from a press release on the website of the Royal College of Physicians [2].

CONCERN 1

> In the 'joint statement' it says, *"It is important to diagnose hypothyroidism with a blood test"* **and** *"Clinical symptoms and/or signs alone are insufficient to make a diagnosis of hypothyroidism"* **and** *"The only validated method of testing thyroid function is on blood, which must include serum TSH and a measure of free thyroxine (T4)"* **and** *"Patients with suspected primary hypothyroidism should only be diagnosed with blood tests including measurement of TSH"* **and** *"There is no indication for the prescription of T4 or any preparation containing thyroid hormones to patients with thyroid blood tests within the reference ranges"* [1].

The 'joint statement' makes the assumption that the use of thyroid function blood tests, which include the thyroid stimulating hormone (TSH) test, in the diagnosis and management of hypothyroidism is infallible, which is contradicted by case studies and certain research. Practitioners including endocrinologists are successfully treating and/or endorsing the treatment of such patients [ie hypothyroid patients with clinical symptoms of hypothyroidism but with TSH tests within the reference range] and have been instrumental in returning such patients to health.

Examples of such hypothyroid patients for whom the TSH test showed inconsistent correlation with their symptoms include the two co-authors of the book 'Hypothyroidism in Childhood and Adulthood, A personal perspective and scientific standpoint', which documents the experiences of identical twin sisters who developed hypothyroidism in childhood [3]. In adulthood, both had their thyroxine [T4] only dose, adjusted and reduced by their general practitioner, so that their TSH appeared within the reference range as the recent statement now recommends. At this reduced level of treatment they developed symptoms of hypothyroidism which were numerous and severe and potentially life threatening. The two patients concerned can no longer tolerate thyroxine [T4] and are now being treated with Armour Thyroid USP, which resulted in their recovery. The provision of Armour Thyroid USP prescriptions on an ongoing basis is necessary for their continued well-being. This treatment regimen with Armour Thyroid USP, which proved to be the optimum treatment for both twins, was initially provided via their private doctor, following a meticulous review of their condition and their individual clinical needs. Eventually, due to its success in enabling both twins to recover, this treatment regimen, was endorsed by their NHS endocrinologist and continued by their NHS general practitioner to date.

The 'joint statement's' assumption regarding the infallibility of the thyroid function blood tests is also contradicted by research eg. Dzurec's research in 1997 which suggested, ***"Individuals may experience thyroid-related symptoms such as fatigue and depression before thyroid indices become abnormal."*** [4]. Furthermore, the above quotes from the 'joint statement' [see Concern 1] in respect of the infallibility of the thyroid function blood tests are further called into question and contradicted by a General Medical Council, Fitness to Practice Panel, who concluded that, ***"The Panel could not be satisfied, on the basis of all the evidence presented, that a therapeutic trial of thyroxine therapy***

was inappropriate for a patient with clinical features of hypothyroidism and with thyroid function tests within the reference range" [5].

- **As the 'joint statement' does not appear to acknowledge the existence of hypothyroid patients with clinical symptoms of hypothyroidism but with TSH tests within the reference range, what contingency has been provided for such patients?**

CONCERN 2

> In the 'joint statement' it says, *"In patients with suspected primary hypothyroidism there is no indication for the prescription of T4 or any preparation containing thyroid hormones to patients with thyroid blood tests initially within the normal range. Thus patients with normal T4 and TSH do not have primary hypothyroidism and even if they have symptoms which might suggest this should not be given thyroid hormone replacement therapy"* [1]

There is concern with regards to the word 'normal' being used in the 'joint statement' as what is 'normal' for one patient is not necessarily 'normal' for another and there is some confusion within the medical profession regarding the terminology, which is being used. Furthermore, there are concerns that a proportion of junior doctors are not consistently confident in drawing conclusions from TSH results, as concluded from a survey published in 2008 by Khromova and Gray [6]

- **Could the authors of the 'joint statement' please state why they insist on the use of the word normal above and explain exactly what they mean by this?**

- **Could the authors of the 'joint statement' explain why they are so certain that such patients are not suffering from hypothyroidism when there is so much evidence available to indicate that such patients are hypothyroid and have recovered their health once they receive the appropriate thyroid hormone replacement therapy?**

- **Are the authors of the 'joint statement' saying that all patients are exactly the same regardless of the cause or degree of their hypothyroidism and so require exactly the same treatment, [that is T4 only], as stated in the joint statement [1] and loudly proclaimed in the RCP press release? [2]**

- **Will existing patients [with clinical symptoms of hypothyroidism but with TSH tests within the reference range], whose health has improved on thyroid hormone replacement therapy now be denied such therapy, when they require such treatment on a continued basis to ensure they do not revert to their previous [pre treatment] levels of ill health.**

- **Furthermore, is such treatment now to be denied to new patients with the possibility of risk of harm to such patients and of condemning such patients to a life of ill health?**

CONCERN 3

In the 'joint statement' it says, *"Some patients, particularly those whose TSH levels are greater than 10mU/l, may benefit from treatment with thyroxine in the same way as for hypothyroidism as above, as indicated in national guidelines…"* [1]

There is concern that the 'joint statement' effectively extends the thyroid stimulating hormone (TSH) reference range i.e. raises the threshold so that hypothyroid patients' TSH must reach 10, before they will be treated (although the average TSH in the population is much less than this).

- **What redress is available for patients suffering from untreated hypothyroidism as a result of doctors following this 'joint statement' [in relation to the extension of the reference range] and thus not providing or discontinuing the treatment of their hypothyroidism?**

- **Does this introduce a two-tier system whereby existing patients who were diagnosed at a TSH below 10 would have their treatment continued but new patients with a TSH below 10 would no longer be treated?**

- **Can the authors of the 'joint statement' explain why in other parts of the world such as the USA, the thyroid stimulating hormone reference range has been truncated, thus ensuring that more hypothyroid patients are diagnosed and receive the optimum treatment for their condition? Conversely, could the authors of the 'joint statement' explain why they have endorsed the extension of the TSH reference range for the UK and provide their rationale for this anomaly?**

CONCERN 4

> In addition, in the joint statement it says, *"Hypothyroidism…should be treated with thyroxine (T4) tablets"* **and** *"Patients with primary hypothyroidism should be treated with T4 using levothyroxine tablets (BNF) alone"* [1].

It is interesting to note that a subset of patients [who do not do well on T4], was a topic for debate within an endocrine nurses training course held relatively recently under the title **"*This house believes that thyroxine is not an adequate form of thyroid replacement in everyone*."** [7].

- **As the 'joint statement' does not apparently acknowledge the existence of hypothyroid patients who cannot recover on synthetic thyroxine only or who are intolerant of synthetic thyroxine, what contingency has been provided for such patients?**

CONCERN 5

> In the 'joint statement it says, *"Overwhelming evidence supports the use of Thyroxine (T4) alone in the treatment of [Primary] hypothyroidism"* [1].

To make a simple analogy, this 'joint statement' is akin to saying that infections should only be treated with penicillin - without taking into account those individuals in society with an allergy to penicillin.

To suggest that just one treatment i.e. thyroxine/ levothyroxine [T4] is the only treatment for hypothyroidism is dangerous to those who have intolerance to synthetic thyroxine and/ or are unable to recover on treatment with synthetic thyroxine only.

A one treatment suits all approach with no definitive medical based evidence and appropriate medical research to back it up is unacceptable. Furthermore, the 'overwhelming evidence' cited, has not been provided and requests for provision of the scientific references used in the compilation of the 'joint statement' have not yet been successful. In addition, attempts to ascertain the identities of the authors of the 'joint statement', so that these issues can be raised with them directly and with clarity have to date been unsuccessful.

- **Please could the authors of the 'joint statement' provide the 'overwhelming evidence' referred to within the 'joint statement'?**

- **And please could the reasons behind this lack of transparency be provided?**

- **Does this lack of transparency comply with the mission statements and standards of the organisations involved?**

- Does the wording of the joint statement comply with GMC best practice guidelines?

CONCERN 6

> The 'joint statement' includes the following; *"We do not recommend the prescribing of additional Tri-iodothyronine (T3) in any presently available formulation including Armour thyroid, as it is inconsistent with normal physiology, has not been scientifically proven to be of any benefit to patients, and may be harmful"* **and** *"The College does not support the use of thyroid extracts or thyroxine and T3 combinations without further validated research published in peer-reviewed journals. Therefore, the inclusion of T3 in the treatment of hypothyroidism should be reserved for use by accredited endocrinologists in individual patients"* [1].

If the argument that Armour Thyroid USP is inconsistent with normal physiology is used against Armour Thyroid USP, since this preparation contains a higher proportion of T3, then the same argument could be used against thyroxine [T4 only treatment], since it contains no T3 at all, nor T1 or T2. Thus, by the same logic, thyroxine [T4 only] would be even more inconsistent with normal physiology.

Further, if the argument that thyroid treatments containing T3 and/or Armour Thyroid USP, have not been scientifically proven to be of benefit to patients and may be harmful to such patients is being used by the Royal College of Physicians and others – then this can be contradicted by scientific evidence that indicates that treatments containing T3 and/or Armour Thyroid USP, have been of benefit to certain categories of hypothyroid patients.

The use of T3 and T4 combination treatment has been shown to be of benefit to patients, by Bunevicius et al. (1999)[8], Bunevicius and Prange (2000) [9] and by Bunevicius et al. (2002) [10]. Other researchers demonstrated that only combined treatment with thyroxine and tri-iodothyronine prevented hypothyroidism in all of the tissues of the thyroidectomized rat, implying that in humans combined treatment with thyroxine and tri-iodothyronine would be necessary to achieve euthyroidism [11].

In 2007, Gautam Das gave Armour Thyroid to three patients who were intolerant to L-thyroxine with a successful outcome and recommend that, ***"a trial of Armour could be considered in patients who have not responded to this conventional treatment…."*** [12]. More recently, in 2008, Lewis et al concluded that, ***"in appropriately selected hypothyroid patients, Armour appears to improve the quality of life in patients who have either had an inadequate clinical response to conventional T4/T3 therapy or are unable to tolerate such therapy"*** [13].

Despite the caveat within the 'joint statement saying, ***"the inclusion of T3 in the treatment of hypothyroidism should be reserved for use by accredited endocrinologists in individual patients,"*** there is concern that, the net effect of the 'joint statement' could be to effectively prevent the prescribing of any treatment for hypothyroidism other than synthetic thyroxine (T4) irrespective of the individual clinical needs of the patients concerned, because of the emphasis elsewhere in the 'joint statement' and the RCP press release that, ***'Thyroxine is the only treatment for primary hypothyroidism'.***

- **Therefore what redress is available for patients suffering from untreated or under treated hypothyroidism as a result of doctors following this 'joint statement' and not providing or discontinuing the treatment of their hypothyroidism with any treatment other than synthetic thyroxine [T4] only?**

- **Does this introduce yet another two-tier system, whereby patients currently being prescribed treatments other than synthetic thyroxine only would have their treatment continued but new patients would no longer be treated with alternatives to synthetic thyroxine – which might be better suited to their individual needs?**

CONCERN 7

> The 'joint statement' says, *"Patients with continuing symptoms after appropriate thyroxine treatment should be further investigated to diagnose and treat the cause"* **and** *"We recommend that those patients whose thyroid blood tests are within the reference ranges but who have continuing symptoms, whether on thyroxine or not, should be further investigated for the non thyroid cause of the symptoms"* [1]

However, in 2000, Tigas et al said, ***" restoration of serum TSH to the reference range by T4 alone may constitute inadequate hormone replacement"*** [14].

In addition, in 2006, Dr A Toft, CBE, MD, FRCP stated, ***"In some patients, a sense of well-being is achieved only when fT4 or TT4 is raised, for example, 30 pmol/l or 170 nmol/l, and TSH low or undetectable"*** [15].

Examples of such hypothyroid patients for whom the TSH test showed an inconsistent correlation with their symptoms include the two co-authors of the book 'Hypothyroidism in Childhood and Adulthood, A personal perspective and scientific standpoint', which documents the experiences of identical twin sisters who developed hypothyroidism in childhood [3]. In their cases, adjusting treatment in accordance with their TSH results rather than their severe symptoms of hypothyroidism resulted in gross under treatment of their hypothyroidism and pursuing this strategy for longer could have resulted in myxoedema coma with resulting mortality risks.

- **As the 'joint statement' does not appear to acknowledge the existence of hypothyroid patients with clinical symptoms of hypothyroidism but with TSH tests within the reference range, what contingency has been provided for such patients?**

CONCERN 8

> In the 'joint statement' it also says, *"We are therefore very concerned that some patients with and without thyroid disease are being inappropriately diagnosed and managed, using thyroxine and other thyroid hormones, in ways which compromise patient safety"* **and** *"However, some patients are inappropriately diagnosed as being hypothyroid (often outside the NHS) and are started on thyroxine or other thyroid hormones which will not only cause them possible harm but leaves the true cause of their symptoms undiagnosed and therefore untreated"* [1].

It is of concern that the 'joint statement' complains that some patients are being diagnosed and treated for hypothyroidism, when according to their blood tests they do not have hypothyroidism or ongoing under treated hypothyroidism, without providing proof that the thyroid function blood tests are infallible or that the patients concerned were not hypothyroid. The claim that patients are being treated for hypothyroidism when according to their blood tests they do not have it has not been substantiated by scientific references.

- **Could the authors of the 'joint statement' explain why patients with clinical symptoms of hypothyroidism but with TSH tests within the reference range, recover their health when treated with the appropriate synthetic or natural thyroid hormone replacement therapy?**

- **Could the authors also explain why, this large subset of patients and/ or their representatives, were not consulted by the development group in relation to the 'joint statement'?**

CONCERN 9

In the 'joint statement' it says, *"There are potential risks from T3 therapy, using current preparations, on bone (eg osteoporosis) and the heart (eg arrhythmia). We note that the extract marketed as Armour thyroid contains an excessive amount of T3 in relation to T4. Overtreatment with T4 when given alone has similar risks*" [1]

Obviously the optimum thyroid hormone replacement treatment has to be prescribed at an appropriate level based on the individual clinical needs of the hypothyroid patient, but research to substantiate the above comments in the 'joint' statement has not been included.

- **Would the authors of the 'joint statement', please supply the appropriate references and research to substantiate the above assertions?**

CONCERN 10

In the 'joint statement' it says, *"The above statements reflect best practice of clinical endocrinologists by the Royal College of Physicians and the Royal College of The British Society of Paediatric Endocrinology and Diabetes"* [1].

If one looks at the guidelines for thyroid function testing (to which this statement refers to on one occasion), originally produced by the Association for Clinical Biochemistry, the British Thyroid Association and the British Thyroid Foundation, they say;
"Routine thyroid function testing has been available for more than thirty years. Therefore, it may be surprising that the quality of evidence to support the recommendations in these guidelines is generally poor…" and ***"There is real need to conduct new studies that conform to the rules of evidence based medicine in order to provide answers to some of the contentious issues in the use of thyroid function testing."*** and
"The document should be considered as guidelines only; it is not intended to serve as a standard of medical care. The doctors concerned must make the management plan for an individual patient" [16]. Therefore, it is of concern that the above caveats have been omitted from the 'joint statement'.

- **Would the authors of the 'joint statement' explain, why the above caveats have been omitted from the 'joint statement'?**

CONCERN 11

If doctors were to follow the recommendations within the 'joint statement', it would mean that the subset of patients who require treatment at a level that suppresses their TSH to feel well and/or who require the treatment with tri-iodothyronine [T3] and/or Armour Thyroid USP to feel well would remain either untreated or under-treated leading to increasing levels of disability and increased risk of myxoedema coma, which has a high mortality rate.

- **Would the authors of the 'joint statement' explain why research which points to the possibility that alternative treatments to T4 can also be very successfully used to treat hypothyroidism have not been acknowledged and given due weight in the 'joint statement'?**

- **Why hasn't the 'joint statement' given due weight to the risks and dangers to hypothyroid patients if their hypothyroidism is undiagnosed/misdiagnosed and hence their hypothyroidism is untreated or under treated?**

The above list of concerns is not exhaustive. However initially, we await your comments to the concerns raised and your replies to all the questions above as a matter of urgency.

Coralie Phillips BSc [Hons] Donna Roach BSc [Hons] Julie Ann Cameron [MBA]

REFERENCES

[1] BTF News magazine - Issue no 67 Winter 2008/2009

[2] http://www.rcplondon.ac.uk/news/news.asp?PR_id=436

[3] Phillips C, Roach D. Hypothyroidism in Childhood and Adulthood A personal perspective and scientific standpoint. Nottingham University Press: 2006.

[4] Dzurec LC. Experiences of fatigue and depression before and after low-dose l-thyroxine supplementation in essentially euthyroid individuals. Res Nurs Health. 1997 Oct;20(5):389-98.

[5] Fitness to Practise Panel, Fitness to Practice Hearing, General Medical Council: 5 September 2007.

[6] Khromova V, Gray TA, Learning needs in clinical biochemistry for doctors in foundation years. Ann Clin Biochem. 2008; 45: 33-38.

[7] Society of Endocrinology, Endocrine Nurses Training Course 9-11 September 2004

[8] Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med. 1999 Feb11;340(6):424-9.

[9] Bunevicius R, Prange AJ. Mental improvement after replacement therapy with thyroxine plus triiodothyronine: relationship to cause of hypothyroidism. Int J Neuropsychopharmacol. 2000 Jun;3(2):167-174.

[10] Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ. Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. Endocrine. 2002 Jul;18(2):129-33.

[11] Escobar-Morreale HF, del Rey FE, Obregon MJ, de Escobar GM. Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology. 1996 Jun;137(6):2490-502.

[12] Gautam Das, Shweta Anand, Parijat De. Does synthetic thyroid extract work for everybody? Endocrine Abstracts (2007) 13 p316.

[13] Lewis DH, Kumar J, Goulden P, Barnes DJ. Improvements in the quality of life in hypothyroid patients taking Armour Thyroid. Endocrine abstracts (2008) 15p359.

[14] Tigas S, Idiculla J, Beckett G, Toft A. Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? Thyroid. 2000 Dec;10(12):1107-11.

[15] Toft A. Understanding Thyroid Disorders. Family Doctor Publications Limited in association with the British Medical Association: 2006.

[16] The Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. July 2006.p.5&68