Sir Richard Thompson KCVO
Royal College of Physicians
11 St Andrews Place
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9 July 2012

Dear Sir Richard,

Thyroid Patient Advocacy's (TPA) avowed aim, since its inception, has been to achieve universal recognition and acceptance for the establishment of a correct protocol for the diagnosis and management of those with symptoms of hypothyroidism.

Existing protocols that run contrary to available evidence cause unnecessary suffering to over a quarter of a million patients in the UK.

TPA's primary objective is to persuade the RCP and other Royal Colleges to give reasonable consideration to introducing a more balanced presentation of the problem into the National Curriculum for basic medical training.

Ultimately, TPA is endeavouring to secure the elimination of insecure practices within the field of Endocrinology, by insisting on:

- More accurate diagnosis of thyroid and thyroid related disease. Progress will be made here when the limitations of current thyroid function tests are accepted, and the matter addressed.

- Acceptance that li-iodothyronine containing medications may restore those patients who do not return to health on thyroxine monotherapy. TPA believes that the Register of Counterexamples to T4-monotherapy supports this approach.

We ask the RCP to give diligent consideration to the extensive literature and research on this subject and to consider revising the present policy statement on medical practice with regard to the diagnosis and management of the thousands of patients in the UK who are needlessly suffering from the symptoms of hypothyroidism.

We await your comments.

Sheila Turner (Chair)

Cc: The GMC, the Royal Society, Secretary of State for Justice, the Treasury Solicitor, Director General WHO; Professor Dame Sally Davies (Chief Medical Officer), the Secretary (and Shadow Secretary) of State for Health, the Presidents of the Society of Biology, RCGP, ACB, SoE, BTA, BSPED, BTF, Royal College of Nursing, the Deans of all Medical Schools, all NHS Endocrinologists, secretary of the Canary Party USA, Deputy First Minister and Cabinet Secretary for Health, Wellbeing & Cities Strategy, Scotland, Shadow Cabinet Secretary for Health, Scotland, Deputy Leader and Health & Wellbeing, Scotland, Professor Sir Iain Chalmers, NHS Ombudsman, Professor David Stott (University of Glasgow)

THE GREAT THYROID SCANDAL

"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". Doctors A. Toft and G. Beckett.[241]

Aims of TPA: To ensure that all sufferers of symptoms of hypothyroidism will be given thorough clinical examination with all relevant biological tests, diagnosed and treated appropriately with medication suited to their needs.

1. Summary: TPA is concerned that the full range of thyroid-related disorders (as opposed to 'thyroid' disorders) remains unrecognised in the UK. Inadequate medical training and a lack of understanding of the greater thyroid system (see Appendix 'A') have led to a failure to offer appropriate and effective treatment for many patients.

2. Situation giving rise to Concern: About 13% of patients in a large UK study prescribed T4-monotherapy continued to suffer symptoms that might, in some way, be related to their T4 therapy,[1,2] So approximately 250,000 patients in the UK do not benefit from the RCP recommended therapy. TPA, having the experience that accords with the test protocol Challenge/De-challenge/Re-challenge (CDR)[3] is collating a 'Register of Counterexamples and triple counterexamples to T4 Monotherapy', [4] (2000 counterexamples July 2012). This Register records patients who continued to suffer symptoms on T4-only, yet found these were mitigated or disappeared when they began T3 hormone therapy. Dr. P. Abernethy, states in *"SIGN 50: A Guideline Developer's Handbook*" (a)…the case of Hunter v. Hanley establishes the customary standard of care for evaluating medical negligence, [5] and (b)… the case of Bolitho v. City and Hackney H.A. found that if the customary standard of care is not logical, the judge is entitled to determine that the defendant's expert's opinion was not reasonable or responsible.[6] The evidence gathered by TPA indicates that Endocrinology's stance and continuance of T4-only treatment is without basis and harmful to thousands of sufferers. [7]

3. Confirming Studies: Studies showing the recommended treatment of T4-monotherapy fails to recognise that not everybody is able to convert T4 to the active T3. [8-15] Doctors are also showing signs of dissatisfaction with T4-monotherapy.[16-19] The RCP have not only disregarded these studies in their policy statement, but also the results of a survey of patients suffering symptoms of hypothyroidism undertaken by TPA (2006)[20] in which 1500 respondents who were undergoing T4-monotherapy were asked "Do you feel that you have fully regained your optimal state of health?" **1176 (78.4%) answered "NO".** The TPA list of counterexamples to T4-monotherapy tabulation,[4] shows there are now more patients who do decidedly better on any combination of thyroid hormone treatment that contains T3 than were participants in confirming studies quoting T4-only treatment. In our understanding of scientific rigour, that simple fact nullifies those T4-only studies.

4. Objective: The RCP should acknowledge that: T4-monotherapy is not an effective treatment for *all* patients and should evaluate available evidence regarding diagnostics and therapy, and the use of the active hormone T3, or thyroid extract, for those unable to regain optimal health on T4-monotherapy.[21-96] TPA urges that a requirement be incorporated within the RCP Curriculum[97] that doctors should be able to demonstrate proficiency in diagnosis and treatment of all thyroid-related disorders, and keep abreast of current research.

5. Method: Systematic criticism of the current approach (RCP Policy) for managing the situation of a suspected defect of thyroid function

a) The Error of Consensus Statements: WHO[98] rates consensus statements as representing the poorest level of evidence, because they fail to recognise new concepts

and treatments based on up-to-date research. It is therefore worrying that the UK official guidelines depend so heavily on "poorest level of evidence" rather than being based on robust science for diagnosis and treatment of those suffering hypothyroid symptoms. [99-103]

(b) *The Linguistic Etiologies of Thyroxine-resistant Hypothyroidism',* [104] finds that the concepts of hypothyroidism and thyroid hormone therapy are unclear in current teaching and Medical Practice Guidelines.[105-111] The RCP (London) defines hypothyroidism as :*"The clinical consequences of insufficient secretion by the thyroid gland".*[112] However, a broader and more helpful definition given by BTA i.e. *"The clinical consequences* of *insufficient levels of thyroid hormones in the body*" includes not only the RCP definition, but also euthyroid hypometabolism (EU) [113-114]

(c) Differential Diagnosis Protocol (DDP): Although the RCP policy statement is about 'The Diagnosis and Management of Primary Hypothyroidism,[112] some of its restrictions go beyond 'primary'. Whilst most patients are diagnosed and treated appropriately, a growing minority are increasingly knowledgeable about, and dissatisfied with their therapy. The RCP should consider all possible causes for those suffering residual symptoms on T4- monotherapy.[113-138] Peripheral thyroid hormone physiology exists, and should be included in the RCP training Curriculum[97] and policy statement.[111] The Differential Diagnosis Protocol[139] requires examination of ALL physical issues and potential causes for symptoms, [140-142] but Endocrinology continues to ignore them. Patients are told their blood tests are 'normal', symptoms are 'non-specific', or they have some other patient-blaming condition. Failure of the RCP to take account of available evidence and research amounts to medical negligence.

The RCP recommends in their policy statement that "*Patients with continuing symptoms after appropriate thyroxine treatment should be further investigated to diagnose and treat the cause",*[112] but fails to indicate what further investigative tests should be undertaken (see Appendix 'A'). In the context of defining failure of the thyroid system, the recording of the Basal Temperature can be useful in providing valuable clinical backup.[143] It is low in hypo-metabolic states, but will rise, albeit slowly, in response to treatment.

6. Misunderstood Science of the greater thyroid system: Endocrinologists attempted to correlate symptoms and signs of hypothyroidism with modern thyroid blood tests in 1997. Results were published in the Journal of Clinical Endocrinology:[144] *"It is of special interest that some patients with severe biochemical hypothyroidism had only mild clinical signs, whereas other patients with minor biochemical changes had quite severe clinical manifestations. Thus, we assume that tissue hypothyroidism at the peripheral target organs must be different in an individual patient. Therefore, the clinical score can give a valuable estimate of the individual severity of metabolic hypothyroidism".* This is an excellent illustration of EH without the authors even knowing it! The genetics of how people are different was published in 2003, but RCP policy does not take account of this.[145]

NOTE: The rare syndrome of THR[146] is physiologically different to EH[113,114] and the two must not be confused.

7. Misleading Policy Statement: The 'AGREE' Instrument,[4] provides an internationally agreed framework for assessing the quality of clinical practice guidelines. Each recommendation should be linked to the references on which it is based. The RCP policy statement fails to supply such references, putting it in question. Each RCP Clinical Guideline Standard[147] and policy statement[112] should have a clearly indicated scientific basis.

8. Misleading Thyroid Function tests: A recently published large-scale analysis studying the health of over 4000 people with mild thyroid failure (SCH) over a 7 year period[144] found long-term treatment with T4 to be very safe in this condition. The younger patients who received treatment had significantly fewer heart problems over the

course of the study, when compared to those whose doctors had decided not to treat them. However, of four T4 v T4/T3 studies (2003),[149-152] T4-only was ineffective for many.[153.p14] Other studies confirm this.[154-158]

9. Misleading and Defective T4/T3 Studies: The authors of the T3-T4 meta-analysis[159] found 501 papers, but rejected 490. The RCP claim the only evidence in the related medical science is contained in 11 randomised clinical trials that compare a T4 monotherapy with combination T4/T3, a claim which TPA would dispute.

An important factor in the design of studies is the choice of subjects, and the comparison. Since these studies are not representative of those with deficient peripheral metabolisms or increased peripheral hormone receptor resistance, they are defective. The focus on the thyroid gland suggests, in the literature, a 14 to 1 exchange because that is the ratio of T4 to T3 in thethyroid gland. Some studies used other ratios, such as 10:1 or 5:1. However, according to Celi,[160] the relative therapeutic value is 3:1, indicating that those on the T4/T3 combination were under-treated. Furthermore, the T3 dosage levels were generally below the starting dose for adults. Moreover, the statistical averaging makes any improvement appear negligible. These studies should now be acknowledged as woefully deficient and discounted.

10. Misleading concept of Normal Thyroid Function and TSH Reference Interval: It is assumed that if the TSH level is within the reference range, then the patient must be euthyroid. This is incorrect because of the phenomena of (a) Central Hypothyroidism and (b) Impaired Peripheral Conversion of T4 to T3 and ineffective cellular utilisation of T3: both of which may be associated with normal tests of thyroid function.

TPA considers that the RCP's upper limit for TSH reference interval of 10.0 mIU/L[112] is incautious and does not fully take into account; (a) the questionable nature of statistics in determining "normality"; (b) relevant background endocrinology science, and (c) controversy attaching to the reference range. TPA would prefer that TSH upper level from 3.0-4.2mIU/L should be considered as the 'grey zone' (borderline increase of TSH), and TSH levels >4.2 mIU/L as definitely elevated, and that this information should be printed on TSH lab reports for clinician guidance.

US Endocrinology 10 years ago, recommended narrowing the TSH reference interval to 0.3 to 3.0 in total contrast to the RCP recommended TSH reference interval of 0.5 to 10.0. Studies link hypothyroidism to diabetes, high cholesterol, increased risk of cardiovascular events, infertility, mortality and risk of future hypothyroidism,[161-164] thus illustrating the grave potential dangers of relying on results within a misleading reference range." 'Central Hypothyroidism' is liable to be missed if raised TSH is taken to be the criterion for determining TH deficiency. The ongoing controversy about the upper limit of 'normal' of 10.0 mIU/L for the TSH test will continue, as suspicion is raised the closer the result reaches 3.0 mIIU/L

Controversy also surrounds those patients presenting with a suppressed TSH. According to the 'TSH Hypothesis' by Warmingham,[165] (supported by the data presented in the McKenna et al. study),[166] when a hypothyroid patient (whose circulating pool of TH is too low) starts taking exogenous TH, a negative feedback system reduces the pituitary gland's output of TSH. This decreases the thyroid gland's output of endogenous TH and despite the patient's exogenous TH's contribution to their total circulating thyroid pool, that pool does not increase until the TSH is suppressed and the thyroid gland is contributing no more thyroid hormone to the total circulating pool. At that point, adding more exogenous TH will finally increase the circulating pool of thyroid hormone. The increase must occur for thyroid hormone therapy to be effective. The patient's suppressed TSH, then, does not indicate that the patient is over-treated with TH; instead, it indicates that the patient's low total thyroid hormone pool will finally rise to potentially adequate levels.

The 'Warmingham Hypothesis' is clear: In general, if doctors deny their patient more exogenous TH because their TSH level is suppressed, they will deny their patient sufficient thyroid hormone to increase the circulating pool of the hormone to a level adequate for maintaining normal TH-driven cellular metabolic processes. But if s/he continues to increase the patient's TH dosage, based on relevant measures of physiological function, such as the basal temperature,[143] then the patient's health will be properly served despite their suppressed TSH level. This hypothesis is of *supreme* importance to the proper treatment and health and well-being of patients suffering hypothyroid symptoms and should be taken into consideration.

11. Misleading Education of Doctors: TPA believes that, in the light of the RCP remit being '*education and maintenance of the professional standard of physicians*',[167,168] the RCP have serious omissions in their curriculum, specifically with regard to thyroid-related problems, resulting in a violation of the requirements laid down by the GMC.[169] This view was corroborated by a recent GP representative for the BTF who apologised, for "*the poor deal patients are getting"* and admitted *"there is still a lot of substandard practice around because of a problem with training & education" and "it's not only knowledge that's lacking – it's experience, training and learning how to manage what is a complex, difficult, and challenging condition*" [170] The RCP should now address the gaps in medical training and knowledge to prevent further unnecessary suffering and harm to patients.

12. Misleading reliance by the GMC on the misled Policy statement of the RCP, resulting in inappropriate disciplining of doctors: The MHRA Review of Unlicensed Medicines' makes 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*".[171] The RCP policy statement and fear of prosecution by the GMC have combined to enforce compliance and take away a doctor's autonomy. Compliance stops doctors diagnosing and treating their patients properly. The RCP policy statement, because it goes beyond the bounds of primary hypothyroidism, is harming patients and compromising doctors' autonomy.

13. Liability of the RCP and GMC in Tort: The Law of Tort requires *inter alia* that individuals, or organisations, should "know or should have known"[172] of available evidence and current scientific knowledge, in order to issue guidance that would not lead to tortfeasance, resulting in harm to patients. The RCP and the GMC have a duty, according to their governance, to apply ethics to their deliberations.. The RCP should know, or should have known of:

- the warnings of the failure of T4 monotherapy. (Kirk & Kvorning, 1947)[173] (Means, 1954) [174] and (Baisier, Hertoghe, and Eeckhaut, Circa 2001)[115]
- the greater activity of T3 over T4. (Gross & Pitt-Rivers, 1952).[26]
- the potential for euthyroid hypometabolism (Goldberg, 1960), showing that intracellular chemistry depends upon T3, not T4.[113,114]
- the discovery of the physiology that connects the thyroid gland to the peripheral, symptom-producing cells. (Refetoff, 1957)[175] and(Braverman 1970) [116]
- that of those treated with T4 monotherapy many remain dissatisfied with their treatment (Saravanan, Dayan).[1,2]
- the existence of numerous subsequent studies on the characteristics of peripheral conversion or metabolism of T4 to T3, and peripheral cellular hormone reception functions.[21-96]
- patient counterexamples to T4-only therapy whose symptoms were mitigated, or went away completely after treatment with T3 was initiated. [4]
- demands of differential diagnostic protocol.[139-142]
- linguistic and logical standards of care.[104-111]
- the very common syndrome of thyroid and adrenal deficiency and the science showing the above syndrome has global effects with imbalance of other hormones, the likely presence of systemic candida and dysbiosis, malabsorption and food

allergy, all playing a probable role.[176]
- using observation and medicine practised as an art[177] as the primary diagnostic method, with the laboratory playing a secondary role.
- their Duty of Care.[168]
- vicarious liability. through the actions of medical practitioners who, following their guidance, are failing to bring patients back to optimal health.

The DoH and medical practitioners believe (wrongly), the RCP's[112] and BTA's[178] statements are scientifically accurate. The continuing belief that T3 is of no clinical value has led doctors into making decisions that adversely affect their patients' health, whereas scientific facts and research have established the efficacy of T3 therapy. Submissions made to BTA by TPA[179] and Dr John Lowe[153] asking that the required amendments be made, have been ignored.

Although medical literature contains at least 22 reports of studies comparing the effectiveness of T4-only, NDT and combined T4/T3,[26,180-190] the BTA cited only two of these papers. One is a review of the studies,[191] the other, a report of a Meta-Analysis.[159] Both contain factual errors, which are specified in Dr Lowe's rebuttal to the BTA.[153] He repeatedly asked the Committee to respond to specific points, but received only an acknowledgment promising further consideration of the matter after consultation with the RCP. We urge that this consultation should now be arranged with a view to a revision of the BTA's statements, which will acknowledge and encompass the scientific facts and research mentioned in this paper.

Summary of TPA concerns:

- There are serious omissions in the RCP curriculum[111] violating requirements laid down by the GMC.[166] There is no reference to peripheral metabolism or peripheral hormone reception physiology (EH);[113,114]
- The Map of Medicine (MoM)[192] gives no guidance regarding recommended diagnostics and treatment of EH, despite the need for other thyroid hormones for some patients
- having been established over 50 years ago.[113-115] The MoM also ignores deficiencies in
- somatic functions[113-142,193-199] and patient counterexamples to T4-monotherapy;[4]
- -There is no validated published research showing that T4-monotherapy is safe and effective for all sufferers, therefore, this proposition by the RCP cannot be relied upon;
- The RCP should declare why, despite the studies showing replacement therapies to be ineffective, even harmful,[153-158] they ignore the existing evidence demonstrated in this paper;
- There has been a notable selectivity in the RCP's appraisal of the medical literature, with particular focus on the efficacy of T3 and thyroid extract, by way of misuse of the ranking of evidence in evidence based medicine (EBM);[200, 201]
- The primary contention appears to be that if there are no, or not extensive formal trials between these different types of preparations, it is concluded that the synthetic preparations are more efficacious;
- Patients' views and preferences were not sought from thyroid support groups other than the BTF, showing bias, before publication of the RCP policy statement;[112]
- Many such patients chronically use more prescription drugs, especially for diabetes, cardiovascular disease, gastrointestinal conditions,[202] depression, anxiety, memory loss and Alzheimer's, all of which can be associated with lower thyroid levels. Research has shown improvement can be achieved with thyroid hormone replacement.[160-165,203-237]
- Results of one study screening for adult hypothyroidism suggested 100,000 people with under active thyroids would benefit from T4 treatment.[238] However, according to the BTA, BTF, ACB et al.[100] screening for thyroid dysfunction in a healthy adult population is not warranted.

Conclusion: The following text is written in recognition of the distinguished position currently held by medicine and its institutions in the mind of the public, a position which one would wish to be maintained, and indeed, enhanced. However, this position of high regard is threatened by the criminal marketing of medications by certain pharmaceutical companies, an activity which is now met with increasing condemnation in the US courts. The leader in this criminal activity has been shown to be the British pharmaceutical company GSK, which has sustained the largest fine ever, anywhere, of 3 BILLION US dollars, for criminal activity.[239] There is now a call for a UK prosecution.[240]

In contrast to this, TPA is currently seeing a situation in which many safe, effective medications are being discouraged from the market place, de facto by threat of prosecution of the prescribing doctors. Within a court of law there may be no legal distinction between the criminality of inappropriate marketing and inappropriate withholding of medication, especially when that medication is safer, cheaper and more effective, than alternatives.

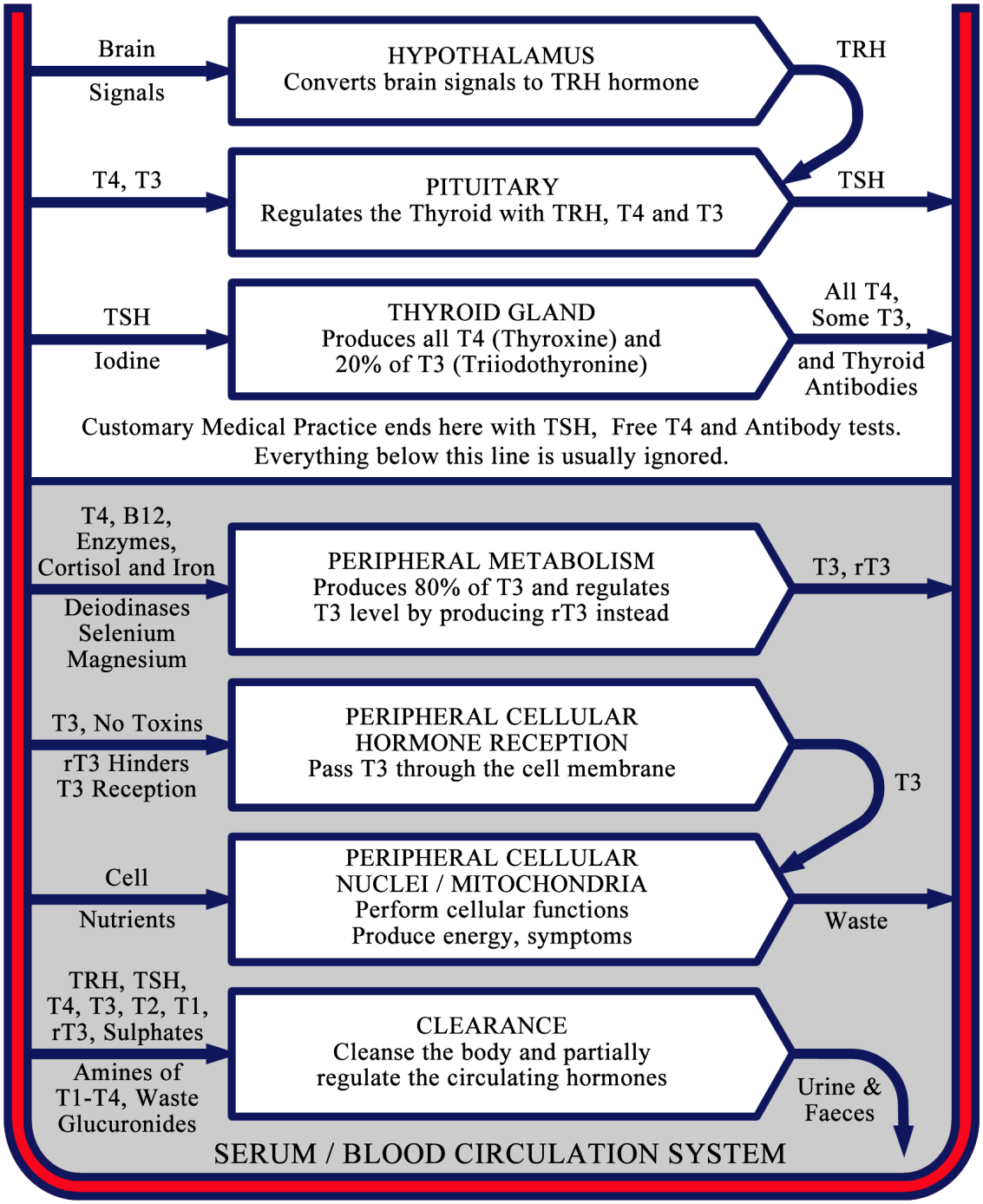
TPA therefore respectfully, but earnestly, urges the RCP to review its policy statement of the scientific evidence for the correct testing and effective treatment of the thyroid system at all levels, thereby improving the quality of life of tens of thousands of patients.

A timely and radical review would be welcomed by an increasingly knowledgeable public, as well as by those physicians currently struggling to provide what they know to be the most appropriate treatment for their patients.

Sheila Turner (Chair) – Thyroid Patient Advocacy

Appendix 'A'

The Greater Thyroid System
(Customary practice ignores the grey area)



Many patients are being denied adequate relief from the symptoms of hypothyroidism because less than half of the greater thyroid system is being considered by physicians. The half which is being considered is not fully tested if the Thyroid Stimulating Hormone (TSH) is 'normal'. This chart illustrates the flow through the system starting at the top of the chart with signals from the brain to the bottom of the chart where the symptoms are sensed.

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