



EDITORIAL

Hypothyroidism: Treating the Patient not the Laboratory

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Is mild to moderate hypothyroidism substantially more common than is generally suspected? Are the standard tests insensitive and inadequate? Is thyroxine not the best treatment? Remarkably, these issues have been raised repeatedly over the last half-century, with no clear answers emerging. Now we hope to cast two small rays of light into this dark and difficult area.

In this issue we publish 2 papers that question the basis of the current diagnosis and treatment of hypothyroidism. Skinner and colleagues from Birmingham examine the effect of thyroxine supplementation on patients with clinical indicators of low thyroid function but normal thyroid biochemistry (p. 115), while Baisier and associates from Antwerp report on the correlation between a number of biochemical tests of thyroid function and both levels of symptomatology and response to treatment (p. 105).

The history of our understanding of acquired hypothyroidism goes back more than 120 years to the description by William Gull in his 1873 paper 'On a Cretinoid State supervening in Adult Life in Women' [1]. It was another 2 decades before Murray reported successful treatment of the disorder with (ovine, injected) ground-up thyroid gland tissue [2]. When this was produced in tablet form, and standardized, it became the staple treatment for hypothyroidism until it was superseded after several decades by T4 [thyroxine]. Although T3 [tri-iodothyronine] was also available, clinicians voted with their pens for T4 because it was longer-acting and therefore easier to stabilize.

Thyroid replacement, often with T3, was of course used quite widely in psychiatry in the first half of this century, to treat depression—and indeed schizophrenia with withdrawal symptoms, and even dementia [3]. Although this fell into disuse soon after the last war, there has, more recently, been a resurgence of interest in its use in conjunction with antidepressants, whether tricyclics or SSRIs, not without justification, as a 1993 survey found 6 clinical studies published since 1970, with an overall prevalence of subclinical hypothyroidism of 52% (29–100%) in patients with depression refractory to 'normal' therapies [4]. This approach, unfortunately, suffers from a logical flaw; subclinical hypothyroidism is defined as the presence of abnormal laboratory tests without clinical signs, but what if, in this context, the refractory depression is a symptom of the hypothyroidism? Of which more later, particularly in the two Clinical Research papers in this issue.

The diagnosis of hypothyroidism is, if anything, more complex and confusing. Until the early 1970s diagnosis had to be confirmed by means such as basal metabolic rate, I^{131} uptake, protein-bound iodine, and perhaps serum cholesterol. None of these was a direct measure of thyroid hormone, so when measurement of thyroxine was introduced it looked like being the solution to every problem. Sadly not, but then TSH measurement arrived close on its heels, and again saved the day, or appeared to do so. But there are still several biochemical problems with these methods of testing, all of which relate to the basics of thyroid biochemistry.

TRH released by the hypothalamus triggers the production of TSH by the pituitary, which in turn stimulates the production and release of the thyroid hormones, T4 and T3. These two hormones are produced in the thyroid in the ratio 4:1 but, firstly, T4 has a greater affinity for TBG, so more dissociated, active T3 is normally present in the blood, and, secondly, T3

is clearly more biologically active. A precise figure is difficult to obtain, as the relative effects on different organs and functions vary, but certainly T3 appears to be 4–5 times more active; a study in 1999, for instance, substituted 12.5 μg of T3 for 50 μg of thyroxine in 33 patients already on T4, and reported improvements in several physical and psychological parameters [5]. Moreover, thyroid production of T3 only represents a small part, perhaps 20%, of total production, because the bulk of T3 is produced in the periphery by conversion from T4 under the influence of several sub-types of the 5-deiodase enzyme. The most active is the type-I enzyme, present mainly in liver and kidney, which was shown in 1991 to contain a selenocysteine molecule, and thus to represent a second essential enzymatic role for selenium [6]. Unsurprisingly, several other nutrients are also considered to be necessary for this process.

The first problem with assessment of thyroid function, then, is that T4 is not the only thyroid hormone, nor the most active, but it is the most common, at least in blood, and hence it is the most useful and economic parameter for routine testing. The second problem is that feedback regulation of TSH secretion is mediated by T4 rather than T3, so TSH cannot be relied upon for a definitive answer. The third problem is that total thyroid hormone activity is more dependent on T3 than T4, and T4 alone is therefore not a good indicator. The fourth is that thyroid hormone levels can be altered, in terms of both actual *in vivo* levels and *in vitro* test results, by a variety of exogenous factors. These include radiation, infections, medications, and environmental toxins such as heavy metals and PCBs [7]. The result is that in contrast to subclinical hypothyroidism (patient normal, laboratory abnormal), which has been relatively well researched, the problem of ‘sub-laboratory’ hypothyroidism (patient abnormal, laboratory normal) lacks even a recognizable name. For these reasons, *inter alia*, researchers have recently become more interested in other means of assessing thyroid function, such as the older indirect indices: Achilles’ tendon reflex, serum cholesterol etc. [8].

There has been an alternative school of thought for almost as long as there has been a conventional one. In Belgium, Eugene Hertoghe first wrote on thyroid treatment in 1915 [9]; remarkably his work has been continued by two succeeding generations of the same family. In the USA Broda Barnes first published on this subject in 1942 [10], although his major work appeared in 1976 [11]. More recently we published a review of the subject in 1996 [12]. The central thrust of all these authors has been that hypothyroidism is widely underdiagnosed, and undertreated, and that over-reliance on laboratory indices has thus misled several generations of doctors, our own included, into failing their patients. In recent years, both Skinner’s earlier paper [13] and the Zulewski paper cited above [8] found little or no correlation between either T4 or TSH and clinical status.

As Skinner characterizes the present state of affairs in this issue: “This arises from a current misconception that evidence-based medicine means laboratory-based medicine.” In other words, we may all be guilty of treating the laboratory rather than the patient. But there may still be effective solutions. The methodologies for measurement of serum T4 and T3 were first described in the early 1970s, and although it has been little appreciated by the medical profession in general, assays for 24-hr urinary T4 and T3 were also described [14, 15], and have been used for some years by a small number of physicians. Walter Baisier in Antwerp has thus been able to review over 800 patients seen since 1984, who were diagnosed, on clinical grounds alone, as suffering from hypothyroidism. He reports a clearly better correlation of clinical status (i.e. symptom score) with T3 excretion than with T4 or TBG ($r^2 = 0.30, 0.12, 0.19$ respectively). He further notes the outcome of treatment with ‘natural’ desiccated thyroid supplements, and the finding that the end-point dosage correlated well with baseline T3 excretion. It is only fair to point out that we requested that reporting of the treatment arm of the study in this paper be restricted to what is of direct relevance to the diagnostic issue.

At a later date we hope that it may be possible to publish studies on the comparative benefits of T4 and T3 supplements. After all, logic dictates that if T3 is the best laboratory

indicator of subjective status, it could be the best therapeutic agent too—although Broda Barnes and a number of others argue strongly for the use of ‘natural’ supplements. For now, Gordon Skinner in Birmingham reports on the use of thyroxine in 139 patients with ‘sub-laboratory’ hypothyroidism followed for 6–12 months. Ninety-three per cent showed significant clinical improvement. Although baseline-free T4 and TSH were normal (as a selection criterion) they both showed a shift with treatment in the direction of improvement. This goes some way towards substantiating his previously stated contention [13] that hypothyroidism should be diagnosed and treated on clinical grounds, even in the absence of laboratory confirmation of diagnosis.

Over the 10 years of publication of the *Journal of Nutritional & Environmental Medicine* we have returned more than once to the question of flawed papers or arguments, and the conflict between innovators and quality controllers. This issue of hypothyroidism is an interesting instance, where the subject is not a single paper but a medical point of view that has been around for much of the last century, without ever achieving thorough substantiation of its hypothesis. We hope that with this issue we can make the still-muddy waters a little clearer. Given current concerns over publication ethics and bias, it is worth stating that as part of the editorial process we have established to our satisfaction that Drs Skinner and Baisier, and myself also, are clinicians, with no vested interests that conflict with the scientific one of publishing these potentially very important findings.

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