Supraphysiological Cyclic Dosing of Sustained Release T3 in Order to Reset Low Basal Body Temperature.

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The use of sustained release tri-iodothyronine (SR-T3) in clinical practice, has gained popularity in the complementary and alternative medical community in the treatment of chronic fatigue with a protocol (WT3) pioneered by Dr. Denis Wilson. The WT3 protocol involves the use of SR-T3 taken orally by the patient every 12 hours according to a cyclic dose schedule determined by patient response. The patient is then weaned once a body temperature of 98.6°F has been maintained for 3 consecutive weeks. The symptoms associated with this protocol have been given the name Wilson's Temperature Syndrome (WTS).

There have been clinical studies using T3 in patients who are euthyroid based on normal TSH values. However, this treatment has created a controversy in the conventional medical community, especially with the American Thyroid Association, because it is not based on a measured deficiency of thyroid hormone. However, just as estrogen and progesterone are prescribed to regulate menstrual cycles in patients who have normal serum hormone levels, the WT3 therapy can be used to regulate metabolism despite normal serum thyroid hormone levels. SR-T3 prescription is based exclusively on low body temperature and presentation of symptoms.

Decreased T3 function exerts widespread effects throughout the body. It can decrease serotonin and growth hormone levels and increase the number of adrenal hormone receptor sites. These effects may explain some of the symptoms observed in WTS. The dysregulation of neuroendocrine function may begin to explain such symptoms as alpha intrusion into slow wave sleep, decrease in blood flow to the brain, alterations in carbohydrate metabolism, fatigue, myalgia and arthralgia, depression and cognitive dysfunction. Despite all thermoregulatory control mechanisms of the body and the complex metabolic processes involved, WT3 therapy seems a valuable tool to re-establish normal body functions. We report the results of 11 patients who underwent the WT3 protocol for the treatment of CFS. All the patients improved in the five symptoms measured. All patients increased their basal temperature. The recovery time varied from 3 weeks to 12 months.

Key words: Thyroid, T3, Wilson Thyroid Syndrome, Chronic Fatigue Syndrome, Fibromyalgia Syndrome.

Wilson's Temperature Syndrome.

The hallmark symptoms of Wilson's Temperature Syndrome (WTS), fatigue, anxiety, depression, headaches, insomnia, and muscle aches — are indistinguishable from Chronic Fatigue Syndrome (CFS), except that WTS requires low body temperature as diagnostic of WTS. WTS patients suffer from a wide range of debilitating symptoms, including persistent or relapsing fatigue, muscle aches, insomnia, cognitive dysfunction, and an overall lack of well-being. Low body temperature, depression, and chronic fatigue indicate a hypometabolic state not unlike that of hypothyroidism (1-2). These symptoms resemble those of conventionally recognized hypothyroidism and of CFS (3-5).

CFS is characterized by persistent or relapsing debilitating fatigue that has continued for at least 6 months in the absence of any other definitive diagnosis. The source of the fatigue is unknown and the illness is not alleviated with bed rest. Symptoms vary from person to person and fluctuate in severity. CFS patients function significantly below their pre-illness capabilities. Their quality of life is considerably affected. Although patients

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experience the illness, the symptoms do not have outward identifying physical manifestations.6

Although WTS does not require the strict definition of fatigue lasting for more than 6 months, it still appears that in most cases the definition is indistinguishable from CFS, except that WTS includes patients who have mild fatigue and it does not require other symptoms to be present at the same time. CFS includes fever as one potential symptom, while WTS requires low body temperature.

Low Body Temperature. Body temperature is controlled by an elaborate thermoregulatory system that modulates heat production and heat loss so that the core temperature is maintained within a narrow range. The thermoregulatory center of the brain is located in the pre-optic region of the anterior hypothalamus (POAH). Neurons in the POAH act as a thermostat and modulate heat production and heat loss to control the body temperature. Heat is produced from both metabolic and physical activity. Basal metabolic rates vary depending upon body mass, age, environmental temperature, thyroid status, ingestion of food and supplements. In a neutral environment the metabolic rate of the body produces enough heat to maintain a core body temperature at 37°C (98.6° F). When the heat content of the body increases or decreases, the thermoregulatory mechanisms become active. These mechanisms involve interactions between the sweat glands and the nervous, endocrine, cardiovascular, and respiratory systems and are collectively termed the thermoregulatory system. Due to daily circadian variations, normal body temperature fluctuates from a lowest of 36.1° C (97° F) between 2:00 and 6:00 a.m. and a highest of 37.8° C (100° F) between 5:00 and 7:00 p.m.

Since many factors can affect the thermoregulatory control, many patients who have low body temperature do not suffer from WTS. Low body temperature in itself is not diagnostic of WTS, without a minimum of one accompanying symptom. However, low body temperature appears as a biological marker that consistently and predictably changes during the progression from illness to health.

Although not always noted clinically, CFS patients often self-report low average body temperatures. This low body temperature has been attributed by some researchers to circadian rhythm disruption.7 However; other researchers have found normal mean core body temperatures in CFS patients. It is possible that the subset of CFS patients who suffer from low body temperature were not represented in this study. Alternatively, because CFS patients experience circadian dysrhythmia as demonstrated by their disrupted sleep patterns and salivary cortisol levels, it is possible that the results in this study were affected by the time of day that the study was performed, rather than the mean average of temperatures taken throughout the day (8-9).

History of Research of T3

T3 Treatments for euthyroid hypometabolism. The use of T3 for patients suffering from euthyroid hypometabolic states was first described in the early 1950s. Euthyroid hypometabolism was described as a group of symptoms very similar to CFS, including fatigue, lethargy, irritability, headaches, and musculoskeletal pain with the absence of any known underlying cause, including normal TSH levels. Studies performed by Kurland, Sonkin, Title, and Morton reported the efficacy of synthetic T3 (liothyronine sodium) in eliminating the symptoms of hypometabolism.

One such study performed by Sonkin prescribed thyroid therapy for 88 patients suffering from euthyroid hypometabolism. He scored the symptoms of each patient for the following symptoms before and after thyroid therapy. The following results indicated that T3 was effective in alleviating euthyroid hypometabolism (See Table 1) (10-12).

Table 1. Euthyroid hypometabolism Symptoms Score (Son King LS)

Complaint	Total	Positive Responses
Fatigue	88	51
Myofascial Pain	63	46
Depression	39	20
Headache	4	3
Nervousness	2	0
Insomnia	3	1

Psychiatric research in the use of T3 on euthyroid patients has indicated that people need a decreased dose of antidepressants when taking T3, and that it is also a rapid, safe and effective way of treating depression that fail to tricyclics.13-14 This might explain why WTS patients notice decreased depression from the WT3 protocol.

Chronic Fatigue Syndrome and Fibromyalgia Syndrome. CFS shares many features with fibromyalgia syndrome (FMS).15 The predominance of pain or fatigue is the primary means of distinguishing between these two syndromes. Precedence for the use of T3 to treat CFS can be found in recent successful FMS studies. One study found that 75.32% of FMS patients experienced decreased tender point sensitivity as measured by algometry after treatment with 75-150 mcg T3 in conjunction with other lifestyle changes, including unspecified increases in

aerobic activity, diet changes and nutrient supplementation (16).

Other studies found that supraphysiologic doses of T3 produced significant improvement in all measured parameters. These included algometer measurement of tender point sensitivity, American College of Rheumatology measurement of pain distribution, Visual Analog Scale measurement of symptom intensity, Fibromyalgia Impact Questionnaire scores, and Zung's Depression Inventory scores. Mean heart rate elevations were noted during treatment as opposed to placebo phases, but there was no report of tachycardia or symptoms of thyrotoxicosis (17-18).

The Center of Disease Control (CDC) hypothesizes that CFS might be caused by an initial trigger, such as a stress in the form of an infectious agent, toxin or illness, that can cause a hit and run situation in which once the trigger has happened, the body shifts into a hypo-metabolic state.19 The hypothesis that a subtle thyroid defect might be a secondary response from the initial trigger of stress has not been fully explored, but it has been well documented that the conversion of T4 to T3 decreases under periods of physical injury, as well as, chronic or acute illness (20-21). However, even after the initial injury to the body has passed, the body sometimes has not yet fully recovered.

Case Study Discussion

WTS Protocol for CFS. We performed an in-house study in which 11 patients diagnosed with CFS were given the WTS protocol. Each patient was given a physical exam and multi-chemistry panel to rule out any other medically identifiable causes of fatigue. We asked patients to evaluate symptoms of CFS numerically before and after treatment. Treatment was considered complete when the patient was able to maintain a body temperature of 98.6° F. The table two presents the results. A value of '10' represents greatest severity of symptoms, while '1' represents the least severity. A value of '0' represents absence of symptoms. Each patient required a different amount of time to achieve normalization of body temperature. Recovery time varied between 3 weeks and 12 months.

A statistical analysis of these results, conducted by Aikin*, revealed significant diferences (See Table 3).

After the treatment is discontinued, normally 3 to 6 months after initiation of treatment, the majority of CFS patients report significant and continued improvement in their symptoms. Most patients experience complete resolution of their CFS symptoms persisting years after treatment has been discontinued. Based on clinical observations, many patients are completely freed of fatigue, depression, muscle aches, and other complaints related to CFS.

In addition, if it is demonstrated that return of oral temperature to 98.6°F correlates closely with restoration of good health in a high percentage of CFS patients, this may indicate that body temperature in itself is a useful biological marker that can be reset to normal. Since many patients who have low body temperature do not have CFS, we do not propose that it in itself is diagnostic of CFS, but rather that it is a biological marker that consistently and predictably changes during the progression from.

Table 2. CFS Sympton Score with WTS Protocol

Patient	Before or After Rx	Fatigue	Headaches	Anxiety	Insomnia	Myalgia	Patient Mean	Patient Temp °F
1	Before	10	10	8	10	0	7.6	97.9
	After	4	5	2	2	0	2.6	98.6
2	Before	10	0	7	0	10	5.4	96.9
	After	0	0	1	0	1	0.4	98.6
3	Before	9	0	5	7	7	5.6	97.7
	After	0	0	5	3	1	1.8	98.6
4	Before	10	0	10	10	10	8	97.6
	After	3	0	2	3	1	1.8	98.6
5	Before	8	9	6	8	0	6.2	97.8
	After	1	2	3	0	0	1.2	98.6
6	Before	10	7	9	7	6	7.8	96.9
	After	0	0	0	0	0	0	98.6
7	Before	10	10	0	10	10	8	97.7
	After	0	1	0	0	0	0.2	98.7
8	Before	8	2	3	6	9	5.6	98.4
	After	2	0	2	6	3	2.6	98.6
9	Before	8	2	6	2	5	4.6	97.5
	After	2	1	5	2	3	2.6	98.6
10	Before	10	10	7	9	7	8.6	96.5
	After	0	0	4	2	2	1.6	98.6
11	Before	8	4	9	9	8	7.6	96.9
	After	4	4	7	4	2	4.2	98.6
Mean	Before	9.18	4.91	6.36	7.09	6.55	6.82	
	After	1.45	1.18	2.82	2.00	1.18	1.73	

Table 3. Statistical Analysis of Symptom Scores after WTS Protocol in CFS Patients

Factor	Mean Change	SE**	P-value*
Fatigue	-7.7	.49	< 0.001
Headache	-3.7	.51	< 0.001
Anxiety	-3.5	69	< 0.001
Insomnia	-5.1	.61	< 0.0001
Myalgia	-5.3	.35	< 0.0001

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**Adjusted for Baseline

T3 Clinical Research

A 2001 study published by Bunevicius et al.22 showed that mood, neuropsychological function, and cognitive abilities were much improved in patients who had taken T3 as opposed to T4 (levothyroxine). Although the participants in the study were hypothyroid, the important aspect in the study was that the patients were already taking exogenous T4 and thus had euthyroid TSH and T4 blood values, but still had hypothyroid cognitive symptoms that were resolved with T3 therapy. It was concluded that T3 had much more of an impact in human physiology than once traditionally thought (22-23).

Thyroid Resistance Not only is it possible that conversion thyroid hormone problem might occur, but there is evidence that thyroid resistance might well be a secondary response to the initial trigger causing CFS. Although the concept of euthyroid fatigue was recognized in conventional medicine in the 1950, it is not until recently that it is gaining acceptance again in the medical literature. Current medical literature is identifying euthyroid patients who exhibit hypothyroid symptoms as thyroid resistance. Thyroid resistance shares many of the same symptoms as CFS, including headaches, anxiety, fatigue, and recurring sore throats.

One postulated mechanism for thyroid hormone resistance found in WTS/CFS might be due to a dysregulation in the type I interferons (IFN-alpha/beta) pathway. This results in a sustained upregulation of 2', 5'-oligoadenylate synthetases (2-5OAS). Patients treated with IFN-alpha/beta therapy usually complain of severe fatigue as a limiting side effect, perhaps due to the same effect. The 2-5OAS, IFN-alpha/beta instigates the expression of three closely related proteins. The amino acid sequences of the 2-5OASL proteins display 96% identity with the partial sequence of the thyroid receptor interacting protein (TRIP). It is hypothesized that the 2-5OASL proteins are TRIPs mechanism of suppressing the TR transactivation and/or possibly destroying the thyroid receptor by the proteasome. This is perhaps how CFS / WTS patients might have normal TSH values yet have a clinical hypothyroid state in CFS/WTS (24).

Another mechanism of thyroid resistance found in CFS might be due to a chronic consumptive coagulopathy, which itself might be associated with chronic infections, such as mycoplasmids, and other microbes. It is suggested that supraphysiological doses of thyroid hormone or anti-coagulants and anti-infective agents might be effective treatments options. Current research has not found any clear association between an infectious agent and CFS.18 However, based on a multi-causal model, it is possible that some infectious agent might be a contributory cause for a certain subset of patients, or that it might be a trigger for CFS even after the infection is gone (25).

Immune system defect might be involved in certain amount of CFS patients. There is evidence of inappropriate cytokine response.18 The etiological cause is still not known. However, it is hypothesized that it might be due to decreased thyroid function. Thyroid resistance has been associated with increased infections, such as chronic sore throats (26).

Stress stimulates the hypothalamic-pituitary-adrenal axis, or HPA axis, which leads to increased levels of cortisol. Increased levels of cortisol inhibit thyroid function.27 Some CFS studies have found cortisol levels to be lower than healthy controls.18 However since studies have not found conclusively that cortisol replacement is an effective treatment, cortisol deficiency as the main causative factor for CFS seems not promising. Low thyroid function has shown to affect cortisol levels (28). Some researchers have found that hypothyroidism increases cortisol levels and others have found that it decreases cortisol levels (29).

In conclusion CFS/WTS might have a variety of causative factors that compromise immune system by stress or other insults that come from viruses, bacteria, toxins, or other triggering agents that upset the body's normal functioning. After the initial insult to the body, CFS/WTS symptoms remain, perhaps due to thyroid hormone resistance or peripheral thyroid hormone conversion problems.

Regardless of the mechanism, WT3 therapy seems to restore metabolism to the vast majority of patients.

SR-T3 Protocol

In the clinical setting, T3 therapy is not used to correct a measurable thyroid hormone deficiency, but rather to recalibrate metabolism and body temperature patterns.

Dr Wilson developed the SR-T3 treatment protocol over a 2-year period via empirical observations of treating patients with intractable fatigue. He subsequently treated

more than 5,000 people over a period of 4 years. The Wilson's Temperature Syndrome (WTS) web site (www.WTSmed.com), established in 1997, and provides information to the general public regarding Wilson's Temperature Syndrome. The web site designates at least 250 doctors in the United States (as well as others in Australia, Canada, Finland, New Zealand, Russia and the United Kingdom) on its list of "Wilson's Temperature Syndrome Treating Physicians." Currently, there is an estimated 1,000 American doctors who use the therapy for fatigue and other WTS symptoms.

Unique Features

The unique features of the Wilson protocol that distinguish it from conventional T3 therapy are that it uses a sustained release form of T3, as opposed to Cytomel, and it is cyclic in its administration, with the dose and cycle-length adjusted according to patient symptomatic response.30 The subjects are treated with Liothyronine compounded in a hydrophilic matrix system, employing hydroxypropyl-methylcellulose (HPMC) designed to be taken every 12 hours. The liothyronine is synthetically made and does not differ from any standard pharmaceutical preparation of T3, except that it is compounded with the sustained release agent methylcellulose. Clinical observation using SR-T3 shows that prolonged exposure to T3 changes patient susceptibility to the drug, necessitating alterations in dose. For example, the first cycle SR-T3 may require 90 mcg of T3 B.I.D to obtain a normal temperature, while the second cycle may require only 45 mcg of T3 to achieve the same temperature. Body temperature is used in determining dosage and cycle length.

The original protocol used liothyronine sodium (Cytomel), but undesirable side effects (e.g., irregular heartbeat and occasional atrial fibrillation) prompted the exclusive use of SR-T3. The SR-T3 produced fewer and milder side effects. There are no known cases of patients suffering from atrial fibrillation with the use of SR-T3 according to the WT3 protocol since its development in 1990.

However, a significant amount of patients still suffer from some symptoms, including increased awareness of heartbeats, heart palpitations, increased heart rate, irritability, shakiness, fatigue, and headaches. These effects are usually successfully treated with a "test dose" of T4. A test dose of T4 is a small dosage (.0125-.025 mg) of Levothyroxine taken to dampen the effects of T3 therapy through competitive inhibition of T3 by T4. T4 has 25% the potency of T3, and administration of T4 usually decreases or eliminates the side effects of T3 therapy within 45 minutes.

The clinical experience of numerous physicians suggests that T3 compounded in a hydrophilic matrix system (sustained release system) in capsules taken every 12 hours provides a predictable, well-tolerated means to influence body temperature patterns and alleviate the debilitating symptoms experienced by WTS patients. Once symptoms improve or resolve, patients are able to wean off SR-T3 therapy. Patients often report no return of symptoms after the treatment has been discontinued. Some patients do relapse, but a very short cycle of SR-T3 will bring them back to normal.

Other important consideration in the metabolic regulation related to proper thyroid hormone function is iodine consumption, absorption and utilization. The main function of iodine is the synthesis, storage and secretion of thyroid hormone. Iodine possesses wide antimicrobial functions and adequate iodine levels are required for proper immune function. Iodine is also present in large amounts in other tissues such as in the breast tissue, salivary glands, brain and extracellular fluids. It is excreted in the urine. Iodine deficiency should be evaluated to avoid secondary physiological dysregulations and its associated risk factors. If deficient, iodine supplementation is indicated. In addition, it must be recognized that the cellular transport mechanism for iodine can be defective and it has been reported that this problem can be corrected with the administration of vitamin C (31).

Long-term Success

The use of T3 outside of the WT3 protocol has not been shown to normalize body temperature. Dr Wilson's clinical experience indicates that long-term success in resetting metabolism and alleviating symptoms using the cyclic SR-T3 therapy proposed for this study seems to be related to holding body temperatures close to 98.6°F for a specified set of time. Patients whose body temperatures have been successfully raised to or near 98.6°F show sustained positive responses after the treatment is discontinued. Patients whose oral temperatures are not successfully raised to that level seem to retain less benefit from the treatment.

It is known that exogenous T3 suppresses T4 levels due to negative feedback inhibition of TSH. It is speculated that T4 suppression is an important effect of the Wilson protocol that is essential to its effectiveness. Often more than one cycle of SR-T3 therapy may be needed to increase body temperature to near-normal values. In many cases, one or more cycles reaching a maximum dose of SR-T3 (90 mcg b.i.d.) fails to raise the patient's temperature to normal. The temperature may reach normal on a subsequent cycle at a lower dose. In such cases, we speculate that greater T4 suppression is achieved with each successive cycle

until the body temperature reaches normal. Serial measurements of serum free T4 may help to elucidate this proposed mechanism.

It is speculated that T4 suppression from repeated cycles of SR-T3 therapy results in lower serum levels of T4 and RT3, and therefore less competitive inhibition of T3. This suppression may increase from cycle to cycle, increasing T3 expression with each cycle. Increased expression of T3 may result in greater T4 suppression until body temperature is finally normalized and the metabolism is "re-calibrated." Once temperature is normalized, decreased SR-T3 is needed on subsequent cycles to maintain normal body temperature. Clinical evidence thus far indicates that patients can safely discontinue the sustained-release T3 therapy and maintain benefits once oral body temperature are held at 98.6°F for a specified set of time. More information can be found at a free internet site (www.wtsmed.com/eManual).

After the treatment is discontinued, normally 3-6 months after initiation of treatment, the majority of WTS patients report significant and continued improvement in their symptoms. Many patients experience complete resolution of their WTS symptoms persisting years after treatment has been discontinued. Based on clinical observations, many patients are completely freed of fatigue, depression, muscle aches and other complaints related to WTS.

Clinical Studies

Most studies on thyroid hormone supplementation have been done using levothyroxine. There is current controversy over the effects of thyroid hormone supplementation on osteopenia. Most studies indicated no effect,32-33 while one study of long term suppressive dose of T4 did show a increase in bone loss (16).

Clinical studies using supraphysiological doses of T3 ranging from 93.75 to 105 mcg daily in euthyroid fibromyalgia, over an 8-month period indicated no change in serum calcium and phosphorous, nor in bone densitometry vs. placebo. However there were higher levels of urinary N telopeptides. Liver function tests were no different vs placebo at 4- month follow-up, \serum creatinine and calcium were also normal, indicating no change in muscle mass. Mean heart rate significantly increased from 68.5 bpm in placebo vs 83.94 bpm in T3 patients during the study. No patients developed tachycardia. There was no significant difference in diastolic or systolic blood pressure in T3 or placebo group. Serial EKG indicated no significance except that the placebo QT intervals shortened within the normal range during T phases (34).

Adverse reactions to liothyronine sodium are generally due to therapeutic over-dosage, and thus are characterized by the typical symptoms of hyperthyroidism (e.g., tachycardia, irritability, nervousness, and increased bowel motility). In rare instances, allergic skin reactions have been observed in patients taking liothyronine sodium.

Resumen

El uso de la formulación de liberación controlada de triiodotironina (SR-T3) en la práctica clínica ha ganado popularidad en la comunidad de médicos con prácticas de medicina complementaria y alterna para el tratamiento de fatiga crónica usando el protocolo (WT3) del cual el Dr. Denis Wilson es pionero. El protocolo WT3 involucra el uso de SR-T3 por vía oral tomadas cada 12 horas de acuerdo a un itinerario de dosis cíclica el cual se determina por la respuesta del paciente. El medicamento se va reduciendo una vez la temperatura corporal del paciente se haya mantenido en los 98.6°F por 3 semanas consecutivas. Los síntomas asociados con este protocolo se le ha dado el nombre del Síndrome de Temperatura de Wilson también conocido por sus siglas en inglés como WTS.

Históricamente se han realizado estudios clínicos usando T3 en pacientes que son eutiroideos basado en valores normales de hormona estimulante de tiroides (TSH). Este tratamiento ha generado controversia en la comunidad médica, especialmente con la Asociación Americana de la Tiroides porque no está basado en el reemplazo de una deficiencia medida de la hormona tiroidea. Sin embargo, al igual que el estrógeno y la progesterona que se recetan para regular los ciclos menstruales en pacientes que tienen niveles normales de hormonas en suero, la terapia con WT3 puede ser usada para regular el metabolismo a pesar de niveles normales de hormona tiroides en suero. Las ordenes médica de SR-T3 se basa exclusivamente en una temperatura corporal baja en la presencia of síntomas.

Cuando la función de T3 está disminuida se manifiestan efectos por todo el cuerpo. Uno de estos efectos incluye una disminución de los niveles de serotonina y hormona de crecimiento y un aumento en el número de receptores de hormonas adrenales. Estos efectos pueden explicar algunos de los síntomas observados en WTS. La desregulación de la función neuroendocrina puede comenzar a explicar síntomas tales como intrusión alfa en las ondas cerebrales lentas del sueño, disminución en el flujo sanguíneo cerebral, alteraciones en el metabolismo de los hidratos de carbono, fatiga, mialgia, artralgia, depresión y disfunción cognitiva. A pesar de todos los mecanismos de control termorreguladores del cuerpo y los procesos metabólicos complejos involucrados, la terapia con WT3 está demostrando ser una herramienta

valiosa en el reestablecimiento de funciones normales del cuerpo.

En este artículo informamos los resultados de 11 pacientes que se sometieron al protocol de WT3 para el tratamiento de CFS. Todos los pacientes mejoraron en los cinco síntomas medidos. Todos los pacientes incrementaron su temperatura basal. El tiempo de recuperación varió entre 3 semanas a 12 meses.

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