Changes of Thyroid and Adrenal Function in Chronic Infections/Lyme disease

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Disclosure Statement

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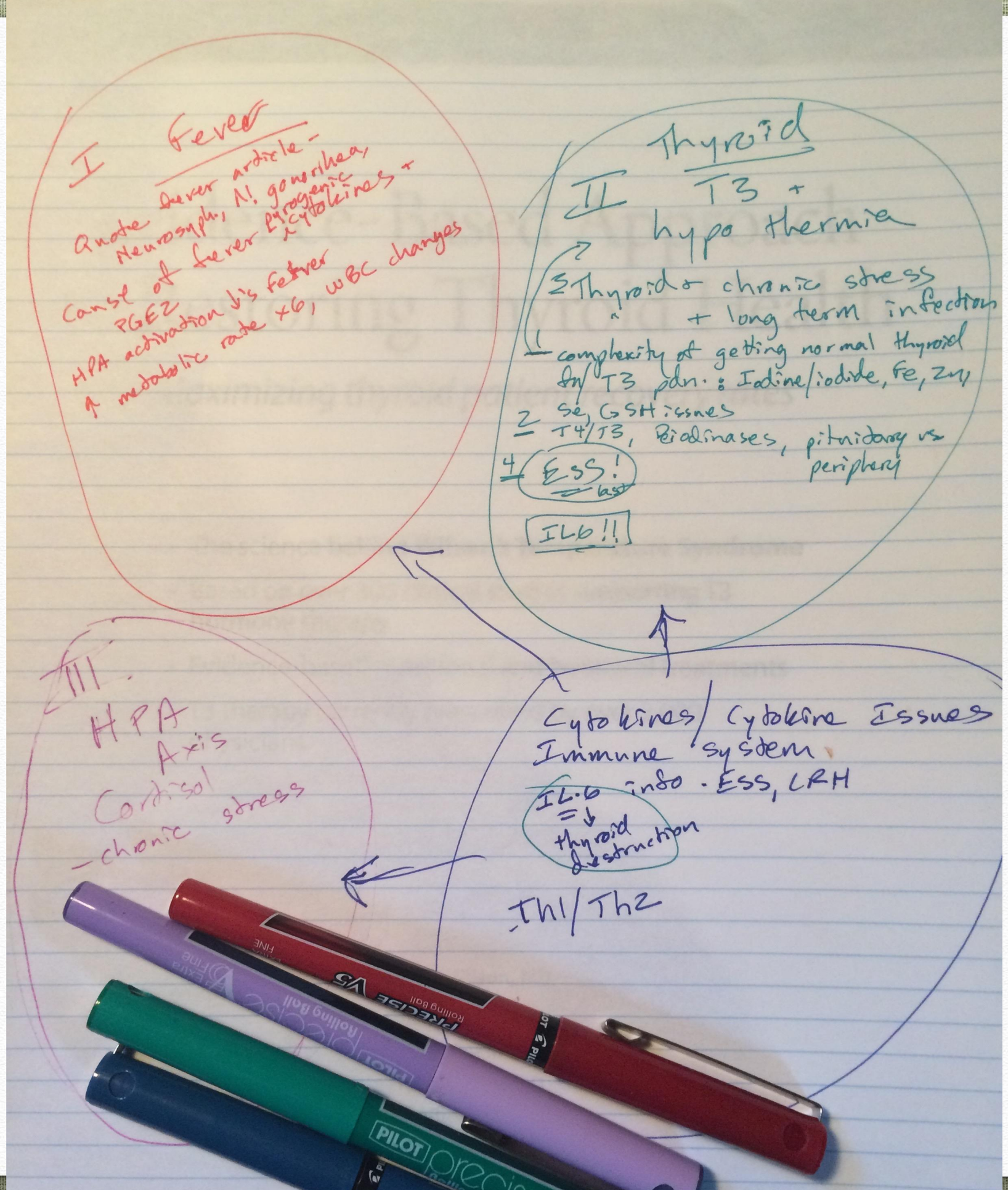

I Fever
Quote fever article -
Neurosyph., N. gonorrhea,
Const of fever Pyrogenic Cytokines +
PGE2
HPA activation ↓'s fever
↑ metabolic rate x6, WBC changes
II Thyroid
T3 +
hypo thermia
Thyroid + chronic stress
+ long term infections
complexity of getting normal thyroid
for T3 pdn.: Iodine/iodide, Fe, Zn,
Se, GSH issues
T4/T3, Deiodinases, pituitary vs
periphery
ESS!
last
IL6!!
III.
HPA
Axis
Cortisol
- chronic stress
Cytokines/ Cytokine Issues
Immune system
IL-6 info - ESS, LRH
=↓
thyroid destruction
Th1/Th2

Preview of topics

- Effects of fever on immune function
- Thyroid function, T3 and hypothermia
- HPA Axis under stress
- Cytokine issues

Fever

- progressive paralysis due to **neurosyphilis** sometimes resolves after an illness associated with high fever
- in 1887, Julius Wagner-Jauregg suspected inoculation with malaria might be a therapy for patients with ‘progressive paralysis’.
- Rationale was, one could substitute an untreatable condition for a treatable one
- this hypothesis was tested in nine patients with syphilitic paralysis by injecting them with blood from malaria patients. Three patients had remission of paralysis.

Young PJ, Saxena M. Fever management in intensive care patients with infections. *Critical Care* 2014, **18**:206

Fever

- further experiments and clinical observations on more than a thousand patients, showed remission of 30% **neurosyphilis**-related progressive paralysis ‘treated’ with fever induced by malaria compared to spontaneous remission rates of only 1%.
- Subsequently, fever therapy was shown effective for gonorrhea. Inducing hyperthermia of 41.7 °C for six hours led to cure in 81 % of cases.
- multiple newer studies of temperature and outcome in various bacterial infections show absence of fever is a sign of poor prognosis in patients with bacterial infections.

Young PJ, Saxena M. Fever management in intensive care patients with infections. *Critical Care* 2014, **18**:206

Fever

- Fever is caused by activation of innate immune system
- production of pyrogenic cytokines: IL 1beta, IL 6, TNF alpha
- release of prostaglandin E2 (PGE2) binds to receptors in hypothalamus to increase body temperature
- Fever is opposed by glucocorticoid (GC) system which has anti-inflammatory properties and down-regulates pyrogenic cytokines
- GC system releases anti-pyretic cytokines

Fever

- Fever increases metabolic rate 6 times above basal levels!!!
- Fever increases neutrophil motility and phagocytosis
- Fever slows growth of intracellular bacteria in macrophages
- Fever enhances binding of lymphocytes to vascular endothelium, facilitating their migration to infection sites
- lymphocyte and macrophage functions are enhanced in physiologic fever range

Fever

- lymphocyte and macrophage functions enhanced in 38 to 40 deg C range (100.4 - 104 deg F), but substantially reduced at ≥ 41 deg C (105.8 deg F)
- 36 º C = 96.8 º F
- 37 º C = 98.6 º F
- 38 º C = 100.4 º F
- 39 º C = 102.2 º F
- 40 º C = 104 º F
- 41 º C = 105.8 º F

Fever

- Human fever temps have been shown to directly inhibit various viral and bacterial organisms. Including: influenza, Strep pneumonia, Neisseria meningitidis (meningococcus)
- Campylobater jejuni isn't pathogenic in birds (body temp 42 deg C) but is pathogenic in humans (body temp 37 deg C). In vitro C jejune growth is much better at 37 deg than 42 deg.
- In animal models anti-pyretic medications are associated with increased mortality from influenza and a variety of bacterial pathogens.

Fever thoughts…..

- Fever is an important defense mechanism during infection
- pathogens preferring lower temperature proliferate better in cooler environs
- optimal temps in vitro: Borrelia burgdorferi 33^{o} (22- 39^{o}), B. garinii 35^{o} (20-40^{o}), B. afzelii 37^{o} (20-41^{o})
- Is it likely patients with physiologic hypothermia are more likely to contract Borrelia?
- Is it possible Borrelia manipulates HPA axis and thyroid systems to lower body temperature?

Hubalek Z, Hlouzka J, Heroldova M. Growth temperature ranges of Borrelia burdorferi sensu lato strains. J Med Microbiol 1998; Oct; 47(10): 929-32.

Thyroid

- normal thyroid function is dependent on many factors
- thyroid hormones regulate: the rate of DNA transcription and expression - i.e. providing instruction manuals and tools for cells to work better
- mitochondrial production of ATP - i.e. energy/metabolic rate

Wilson D. Evidence-Based Approach to Restoring Thyroid Health. 2014.

Thyroid Hormone production

- Iodide must be kept in reduced form in thyroid follicular cells. If iodide increases, will cause autoimmune thyroid disease
- Thyroid tissue is dependent on glutathione (GSH) to keep hydrogen peroxide levels low
- free hydrogen peroxide in thyroid gland initiates autoimmune thyroid disease
- variety of toxics deplete GSH: metals, persistent organic pollutants, PCB's, phthalates

Nutrients and Thyroid function

* Selenium: need 400 mcg per day. If Selenium deficient, then GSH is depleted. (ex: PNW rain depletes Se in soils)

* Iodine intake of less than 50 mcg per day will cause goiter, Iodine therapy can reverse goiter

* BUT iodine supplementation in those with iodine deficiency can cause autoimmune thyroiditis - Hashimoto's or Graves disease

Rose NR, Bonita R, Burek CL. Iodine: an environmental trigger of thyroiditis. Autoimmun Rev. 2002 Feb: 1(1-2): 97-103.

Nutrients and Thyroid function

* iron is critical, target for optimal thyroid function is ferritin of at least 70

* Zinc is used in multiple places in thyroid.

* In patients with nodular goiter, serum zinc levels correlate negatively with thyroid volume.

Thyroid hormones

* T4 is a pro-hormone
* T3 is the active hormone
* Hormone production by the thyroid gland: 92% is as T4
* thyroid gland output is less than 8% as T3
* T4 is the stable transport form, but is inactive at cellular sites

Thyroid - Deiodinase enzymes

* deiodinase enzymes determine intracellular activation and deactivation of thyroid hormones

* each deiodinase enzyme changes behavior in changing physiologic conditions

* impact of thyroid hormones varies by tissue type

Thyroid - Deiodinase enzymes

* 3 deiodinase enzymes: D1, D2, D3
* T4 has 4 iodines
* T3 and reverse T3 (rT3) both have 3 iodines
* T2 and T1….

Thyroid - Deiodinase enzymes

D1	converts T4 to T3 in periphery 12 hour half life	plasma membrane, responsible for serum T3
D2	converts T4 to T3 20 to 40 min half life	intracellular, proximate to cell nucleus
D3	converts T4 to reverse T3, competes with T4 to T3 conversion	not present in pituitary

Raising body temperatures using T3

- T3 is the final active intracellular thyroid hormone.
- T3 promotes gene transcription
- T3 promotes ATP production
- T4 is stable in circulation, essentially, it's a delivery method
- but, intracellular receptors don't use T4

Raising body temperatures using T3

- once inside the cell, T4 must be transformed to T3
- this conversion is governed by de-iodinase enzymes (remember T4 has 4 iodines, T3 has 3 iodines)
- de-iodinase enzymes can convert T4 to either T3 or the inactive hormone, reverse T3 (rT3)
- rT3 slows everything down
- rT3 preferentially binds to T3 receptors

Hypothermia adversely affects immune function

* temperature measurements of patients with chronic Lyme disease show prevalence of average temps < 98.0
* many of these patients have ave. temps below 97.0
* what if my recipe calls for 350^{o} oven, but my oven only gets to 325^{o}?
* in Lyme patients we depend on WBCs mobilizing to protect the patient. What if WBC function is dependent on normal body temperature?

T3 aka liothyronine

* addition of Rx T4 provides more substrate for intracellular production of reverse T3
* patients given T3 feel better 😍
* they sleep better and they poop better 😉
* they have more energy 😄
* T3 may cause tachycardia and fluid retention
* Keep the dose at or below 75 mcg Q 12 H for cycles and at or below 30 mcg Q 12 H for flat dosing

Thyroid lab tests

- pituitary cells lack D3 and therefore lack reverse T3,
- serum TSH reflects what pituitary sees, i.e. periphery could be very deficient in T3 before pituitary notices
- D1 produces serum T3, but not intracellular T3
- there is no lab test that measures intracellular T3 or intracellular rT3
- serum T4 is meaningless if T4 is being converted to rT3

HPA axis

- HPA axis = hypothalamic-pituitary-adrenal axis
- immune inflammatory response has significant brain regulation through HPA axis
- AKA the “Stress System”, activation of HPA axis **end point is glucocorticoid secretion**
- glucocorticoids (GC’s) modulate the stress response
- GC’s alter gene expression
- GC’s alter gene transcription and translation

Neuroendocrine stress response

- Central effectors are corticotropin releasing hormone (CRH) …. and locus coeruleus norepi sympathetic nervous system
- cytokines and inflammatory mediators stimulate hypothalamic release of CRH
- CRH causes pituitary to release adrenocorticotropic hormone (ACTH)
- ACTH causes adrenal GC pdn and release
- adrenal GC's control immune response - inhibit cytokine pdn

Neuroendocrine stress response

- HPA axis has normal diurnal variation as well as being increased during times of stress
- arginine vasopressin (AVP) is synergistic with CRH
- AVP increases ACTH and hypothalamic pro-opiomelanocortin (POMC) derived opioid peptides
- opioid peptides: beta endorphin and dynorphin provide:
  - analgesia, inhibit stress response by reducing hypothalamic CRH
- note: naloxone (naltrexone) blocks beta endorphin and dynorphin

Neuroendocrine stress response

- neurons that produce CRH, AVP, and the locus coeruleus-nor-episystem are:
  - stimulated by serotonergic
  - simulated by cholinergic
  - inhibited by GABA/benzodiazepines
  - inhibited by opioid peptide system
  - inhibited by GC, ACTH, CRH
- BUT - at local inflammatory sites CRH and AVP are pro-inflammatory.

Neuroendocrine stress response

- CRH has central anti-inflammatory and opposing peripheral pro-inflammatory effects
- in some conditions CRH is high in inflammatory exudates. examples:
  - rheumatoid arthritis synovial fluid
  - thyroid follicular cells in autoimmune thyroiditis

Neuroendocrine stress response

- CRH stimulation increases somatostatin and inhibits TSH production and secretion
- increased GC levels inhibit conversion from T4 to T3
- chronic stress activation cases Euthyroid Sick Syndrome
- ongoing CRH stimulation causes increased vigilance, anorexia, decreased libido, changes in motor activity

GC receptors

- type 1 = mineralocorticoid receptors (MR)
  - high affinity for GC's, 10X > than type 2
  - mediate non-stress circadian fluctuations
  - primarily activational
- type 2 = glucocorticoid receptors (GR)
  - low affinity for GC's
  - mediate stress levels of GC's
  - inhibits some systems and activates other systems

Glucocorticoids

- GC receptors are widespread in tissues
- Major effect of GC's = cytokine inhibition
- GC's directly decrease transcription of IL-6 and IL-1 beta
- GC's inhibit pro-inflammatory transcription factors
  - potent inhibition of NF-kappa B
  - and activating protein 1, (AP-1)

Cellular Stress Response

- GC's inhibit functions of all inflammatory cells
  - change transcription of cytokine genes: TNF, IL-1, IL-6
  - inhibit production of arachidonic acid derived pro inflammatory substances, leukotrienes and prostaglandins
- TNF alpha, IL-1, IL-6 are all potent activators of inflammation that stimulate the HPA axis
- GC's inhibit TNF alpha, IL-1, IL-6, but IL-6 is resistant to GC inhibition

Glucocorticoids cause:

- lympholysis and lymphopenia by reduction of IL-1 and IL-2 synthesis
- reduce circulating monocytes by inhibition of IL-1, IL-6, TNF alpha
- reduce eosinophil numbers and adherence secondary to reduced IL-1
- basophils reduced by 80%
- impaired synthesis of collagenase and elastase which reduces degradation of fibrin and extracellular matrix by monocytes

Glucocorticoids cause:

- impaired release of histamines and leukotrienes
- reduced cytokine release from T-Lymphocytes
- increase in circulating neutrophils due to impaired endothelial adhesion
- decreased prostaglandin, leukotrienes, platelet activating factor

interleukins and glucocorticoids

- IL-6 is potent stimulator of ACTH and glucocorticoids
- IL-6 is synergistic/multiplicative with CRH
- IL-6 stimulates AVP
- glucocorticoids upregulate IL-6 production
- cytokine output with prolonged stressors induce GC resistance.

Cytokines

- Immune system affects the endocrine system via cytokines, small glycosylated proteins
- cytokines can be secreted by all cells,
- cytokines confer cellular resistance,
- cytokines mediate communication between immune and non-immune cells
- main sources of cytokines are: macrophages, glial cells, neutrophils, lymphocytes, adipocytes
- cytokines are secreted by thyroid follicular cells

Cytokines

- cytokines affect target cell activation, growth and differentiation
- serve as molecular messengers between cells
- have either pro- or anti- inflammatory effects
- up-regulate inflammation by stimulating T and B lymphocytes - causing antibody production and tissue injury
- cytokine production by thyroid follicular cells can lead to Hashimoto's, post partum thyroiditis
- osteoporosis and diabetes mellitus type 1 are other cytokine mediated endocrine diseases

Cytokines

- hypothalamic-pituitary-adrenal axis activated in inflammation or infection
- mediating cytokines in HPA axis activation:
  - TNF alpha, IL-1, IL-6 which stimulate CRH neurons of hypothalamus
  - creating release of ACTH and glucocorticoids
  - TNF alpha, IL-1, IL-6 increase body temperatures and other signs of illness
  - catecholamines stimulate IL-6 secretion

interleukins and glucocorticoids

- IL-6 activates CRH neurons in hypothalamus
- but, chronic IL-6 acts directly on pituitary and adrenal cells????
- GC's inhibit IL-6 feedback loop
  - increases in cortisol will decrease IL-6
  - increases in IL-6 will increase cortisol
  - acute drops in cortisol will cause 4 to 5x increases in IL-6 and TNF alpha
  - GC replacement gives dramatic decrease of IL-6 and relief of symptoms

Euthyroid Sick Syndrome

- ESS = thyroidal hormonal alterations during non-thyroidal illness
- conditions associated with ESS:
  - MI,
  - systemic inflammation,
  - starvation,
  - sepsis,
  - surgery/trauma,
  - chronic degenerative disease
- AND ———>

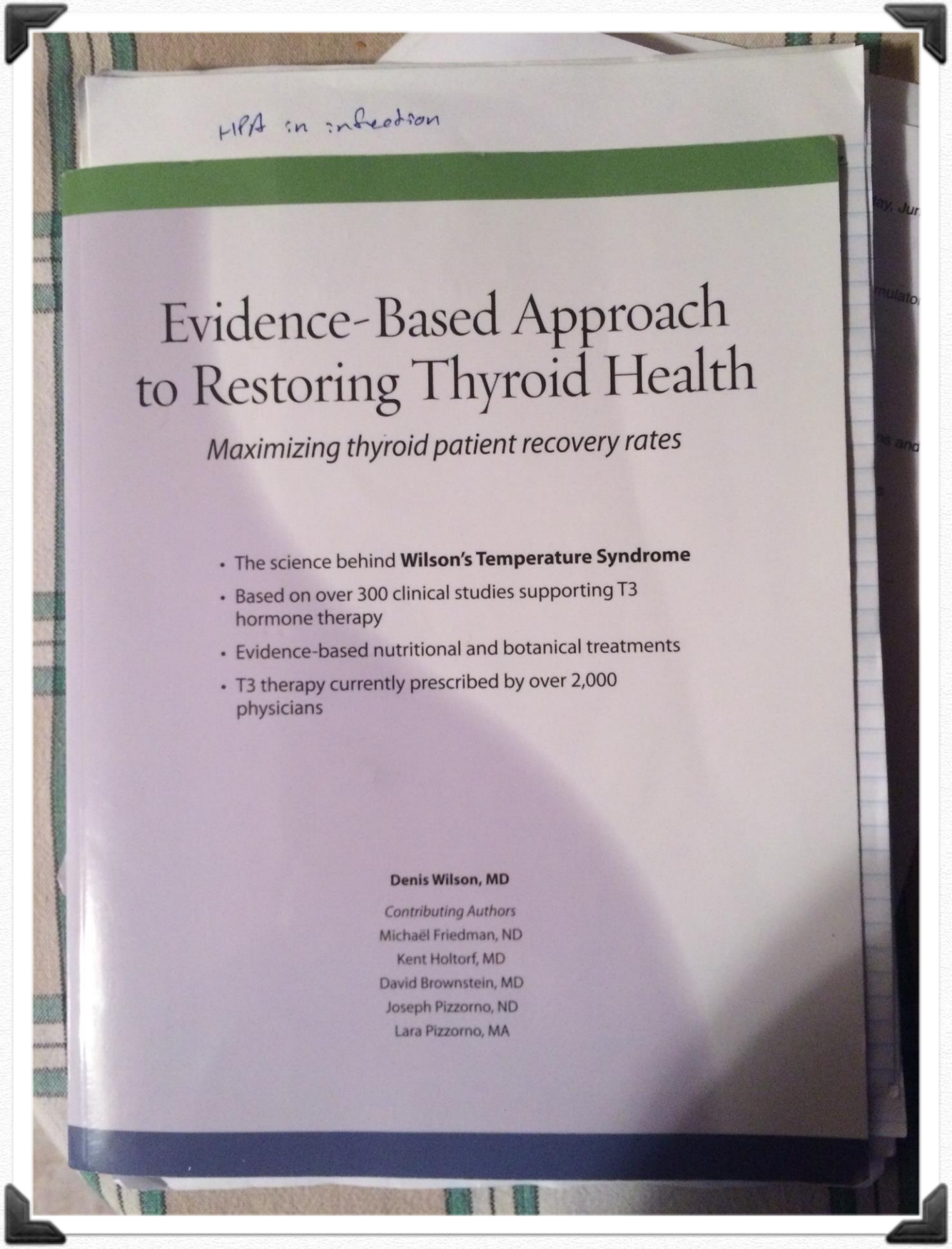
Euthyroid Sick Syndrome

"every other condition with the clinical manifestation of severe illness"

–Boutzios G, Kaltsas G. Immune system effects on the endocrine system. Endotext. March 2015.

Clinical Rationale

- If one of the problems of Borrelia infection is that the immune system fails to mount an effective response….
- If WBCs are 6x more active in fevers/hyperthermia?
- and if Lyme patients have hypothermia?
- What if we raise body temperatures with T3?
- Would WBCs get more active and would patients feel better?


HPA in infection
Evidence-Based Approach
to Restoring Thyroid Health
Maximizing thyroid patient recovery rates
• The science behind **Wilson's Temperature Syndrome**
• Based on over 300 clinical studies supporting T3 hormone therapy
• Evidence-based nutritional and botanical treatments
• T3 therapy currently prescribed by over 2,000 physicians
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WILSON'S TEMPERATURE SYNDROME

Temperature/Treatment Log

Month: _____

Directions: Mark each of the 3 daily temperatures with a '/' and the average with a 'O' (comments/symptoms may be written in vertically)

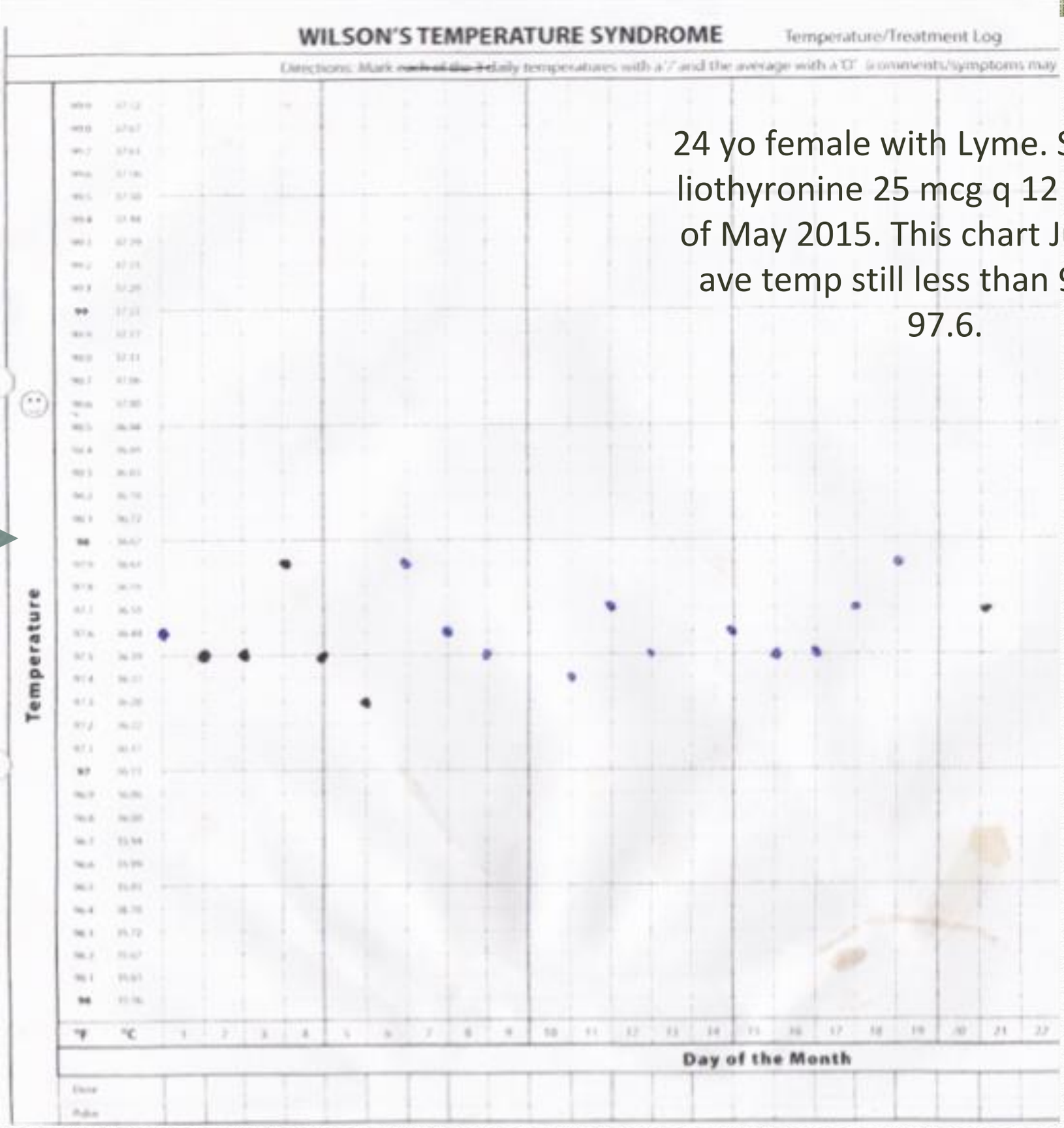
°F	°C
99.9	37.72
99.8	37.67
99.7	37.61
99.6	37.56
99.5	37.50
99.4	37.44
99.3	37.39
99.2	37.33
99.1	37.28
99	37.22
98.9	37.17
98.8	37.11
98.7	37.06
98.6	37.00
98.5	36.94
98.4	36.89
98.3	36.83
98.2	36.78
98.1	36.72
98	36.67
97.9	36.61
97.8	36.56
97.7	36.50
97.6	36.44
97.5	36.39
97.4	36.33
97.3	36.28
97.2	36.22
97.1	36.17
97	36.11
96.9	36.06
96.8	36.00
96.7	35.94
96.6	35.89
96.5	35.83
96.4	35.78
96.3	35.72
96.2	35.67
96.1	35.61
96	35.56

Temperature

°F	°C	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Day of the Month																																
Date																																
Pulse																																

Pt #	prior thyroid Dx	cycle or flat dosing?	better since T3	worse since T3	no change/ unknown
1	no	cycle x2	x		
2	no	flat	x		
3	no	cycle	x		
4	no	flat dosing	x		
5	no	flat dosing	x		
6	no	both	x		
7	yes	flat dosing			x
8	no	flat dosing	x		
9	?	both	x		
10	yes	cycle	x		
11	no	flat dosing	x		
12	yes	flat dosing	x		
13	no	flat dosing	x		
14	yes	flat dosing	x		
15	no	both	x	x	
16	no	flat dosing			x
17	no	cycle	x		
18	no	cycle x2 and flat	x		
19	yes	flat dosing	x		
20	no	cycle x2	x		
21	no	flat dosing	x		
22	no	flat dosing	x		
23	yes	both	x		
24	no	cycle and flat	x		
25	no	both	x		
26	no	flat dosing	x		

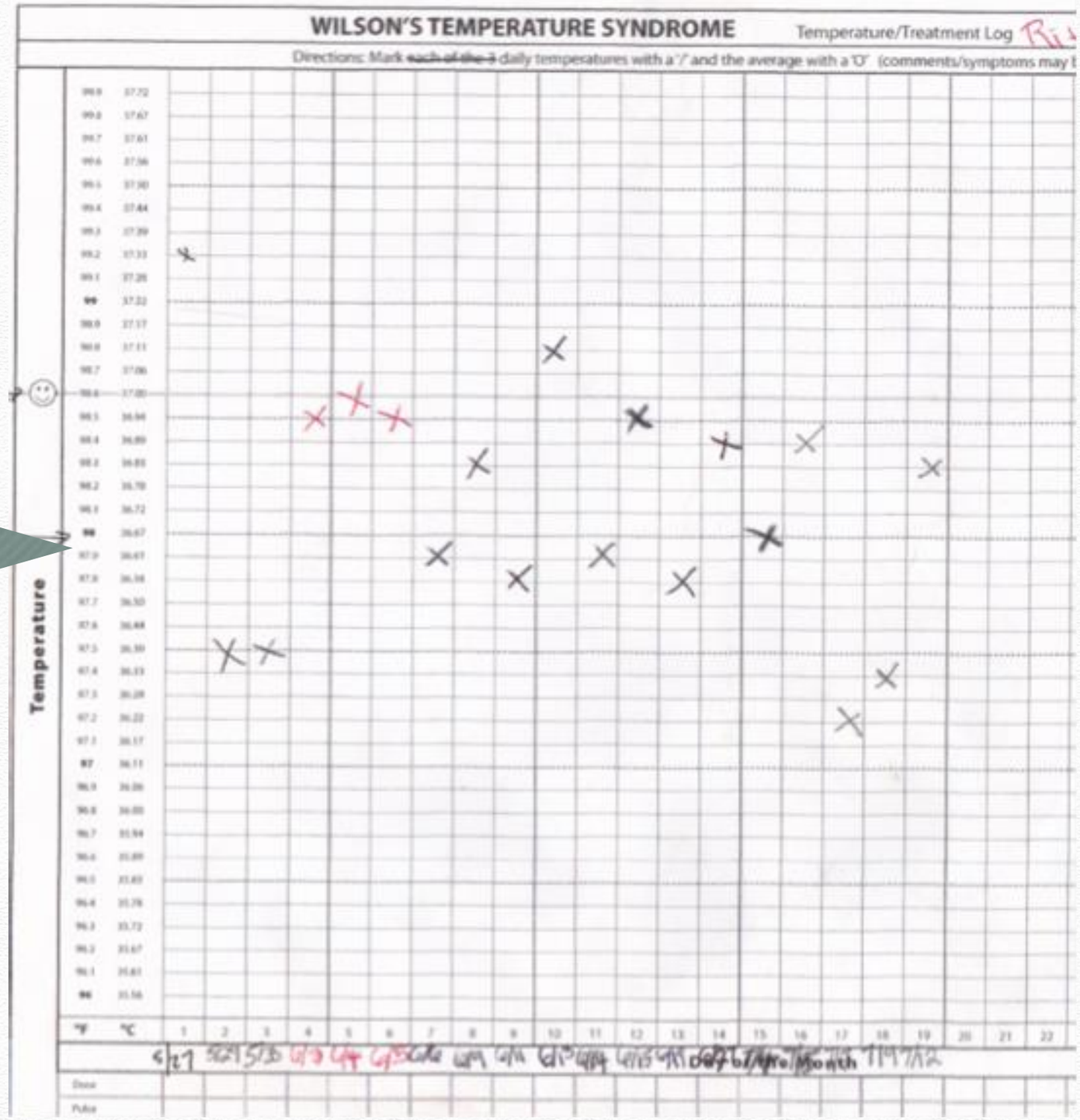
total # patients	**26**
# of patients improved with addition of T3	23
% of patients improved on T3	88%
# of patients unchanged or worse with addition of T3	3
% of patients unchanged or worse	12%



24 yo female with Lyme. Started on liothyronine 25 mcg q 12 h the end of May 2015. This chart July. Note: ave temp still less than 98.0 at ~ 97.6.

98.0

98.0

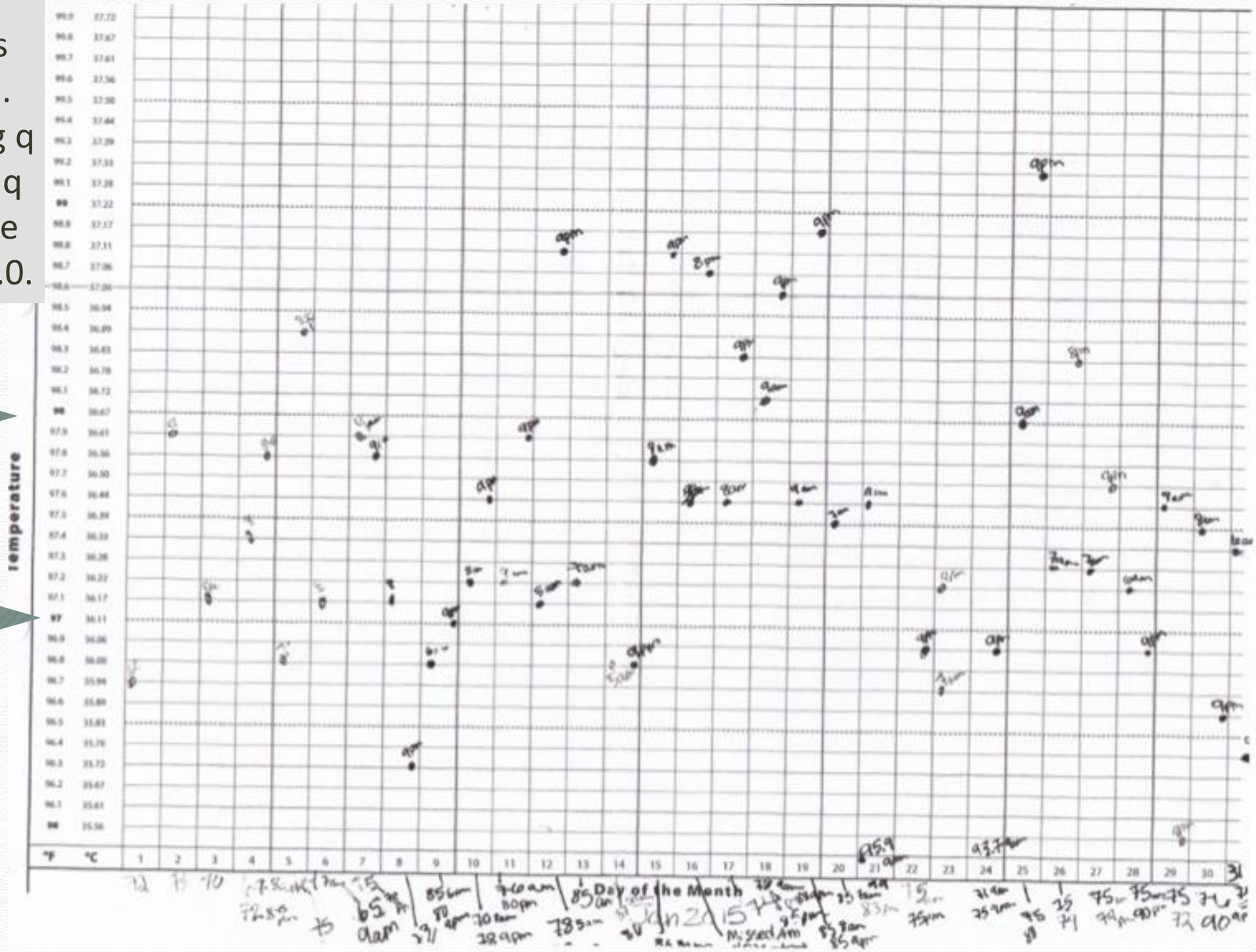


27 yo female, with Lyme and Bartonella. Started liothyronine 5 mcg q 12 h end of May 2015. This chart goes from May to mid July.

34 yo female with Lyme and multiple food and resp allergies. Wilson's cycle dosing of T3. Doses start 7.5 mcg q 12 h up to 75 mcg q 12 h. Note multiple temps less than 96.0.

98.0

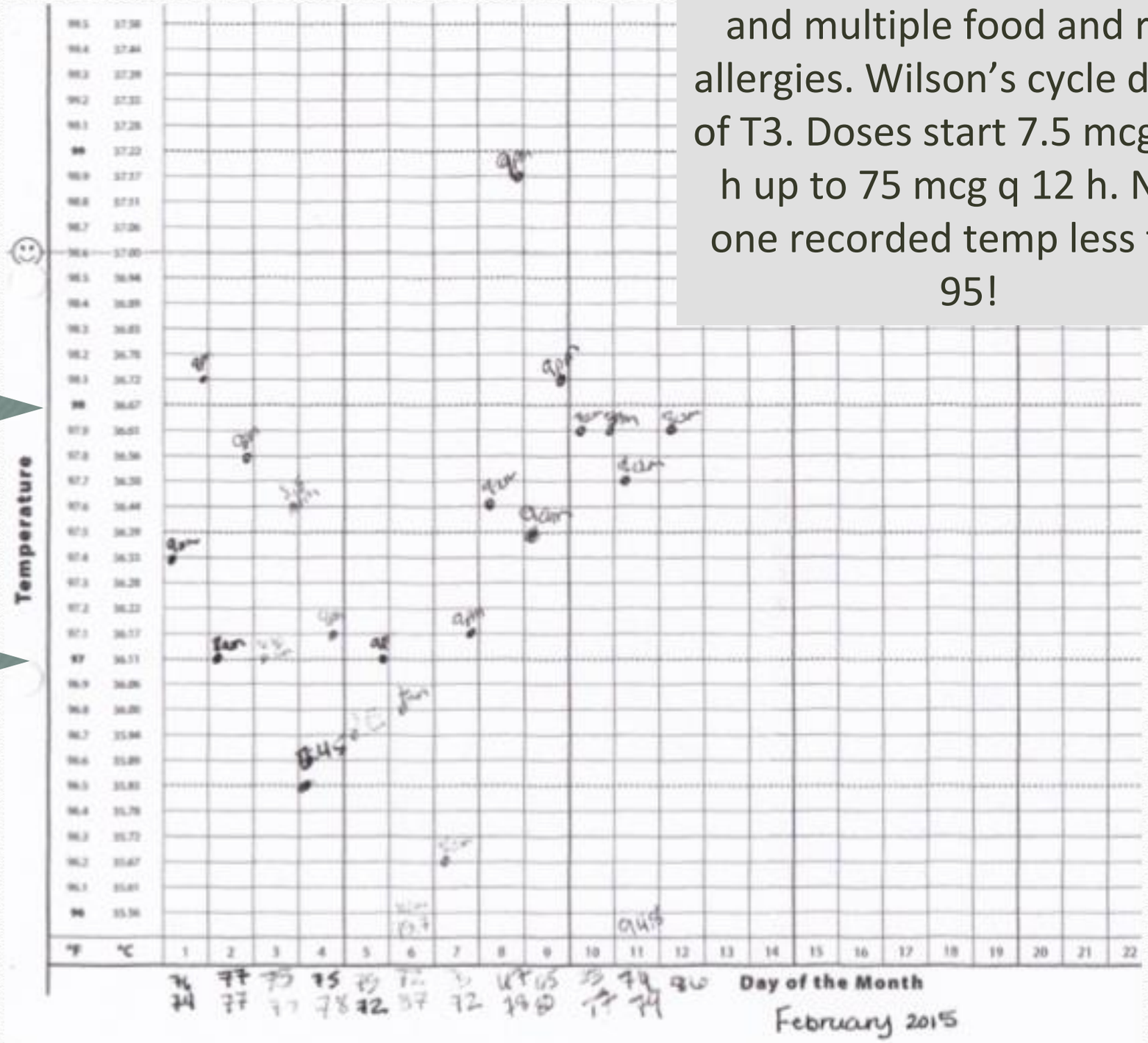
97.0



Same 34 yo female with Lyme and multiple food and resp allergies. Wilson's cycle dosing of T3. Doses start 7.5 mcg q 12 h up to 75 mcg q 12 h. Note one recorded temp less than 95!

98.0

97.0

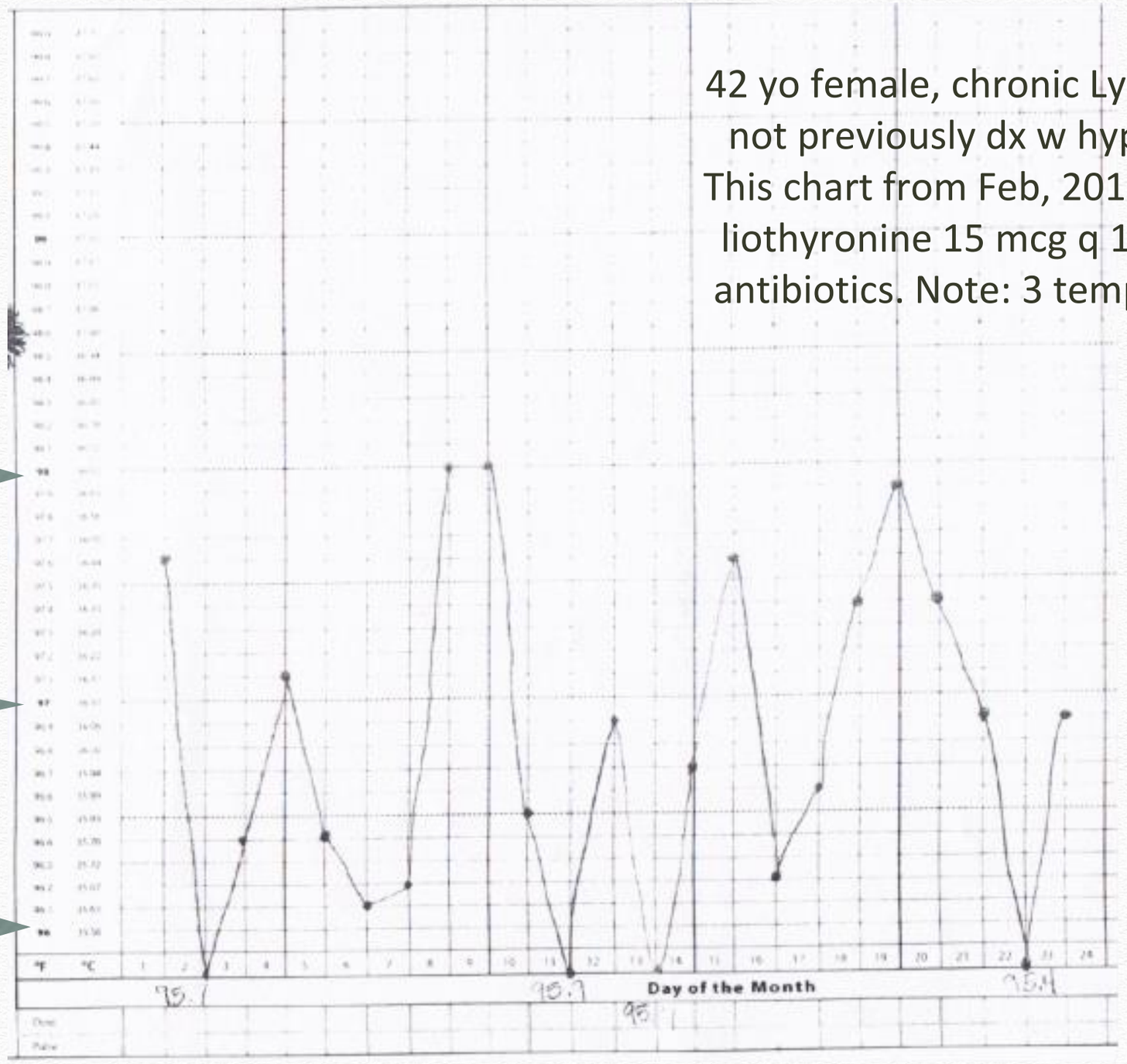


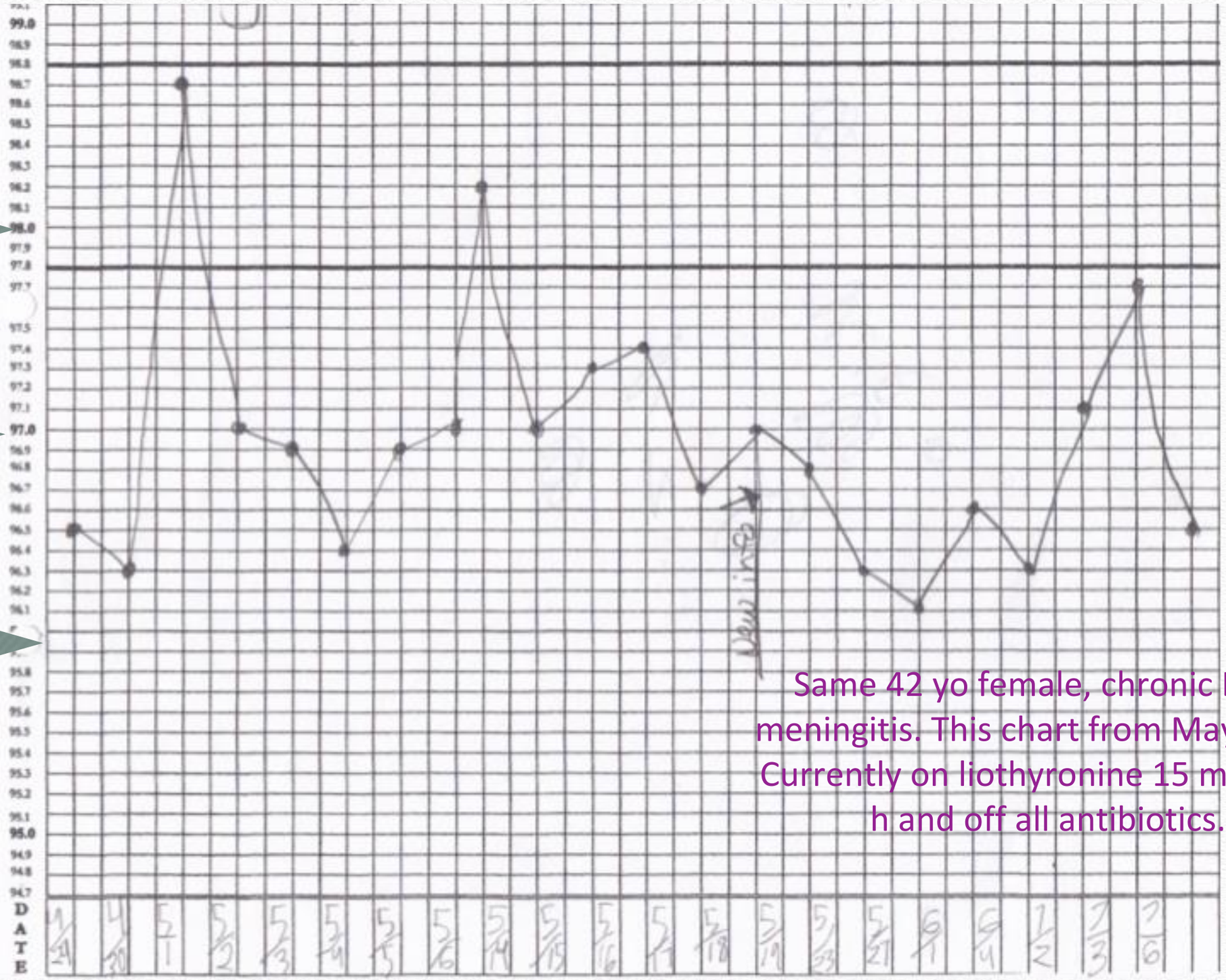
42 yo female, chronic Lyme meningitis, not previously dx w hypothyroidism. This chart from Feb, 2015. Currently on liothyronine 15 mcg q 12 h and off all antibiotics. Note: 3 temps <u>below</u> 96.0.

98.0

97.0

96.0





Same 42 yo female, chronic Lyme meningitis. This chart from May, 2015. Currently on liothyronine 15 mcg q 12 h and off all antibiotics.

Issues with using T3

- Wilson's Temperature Syndrome protocol, cycling doses
- increase daily, plateau at dose high enough for several days that provides total thyroid replacement
- decrease dose every 3 days
- this protocol predictably raises body temperature, at least temporarily
- goal is to get patients off thyroid medication entirely
- dosing regimen is complex and difficult for Lyme patients

Issues with using T3

- generic is Liothyronine comes in 5, 25, 50 mcg
- some patients are sensitive to tableting ingredients in liothyronine and need T3 from compounding pharmacy
- side effects tachycardia, rarely fluid retention
- very short half life, need 12 hour dosing for it to work
- I usually start patients on 10 mcg Q 12 H

Issues with using T3

- If patients are staying on any thyroid medication for more than 2 months they will need adrenal support
- choices are:
  - botanicals: Withania (Ashwagandha), Rhodiola, Eleutherococcus (Siberian ginseng), Lepidium (maca), Cordyceps, Glycyrrhiza (licorice)
  - desiccated adrenal gland
  - hydrocortisone 5 to 10 mg per day with breakfast
- products with herbs and desiccated adrenal:
  - Adrenal Support
  - Cortrex
  - Adrenal Stress End

- Endotext articles:
  - Trianti-Dimoleni V, Mastorakos G, Nezi M. Corticotropin Releasing Hormone and Immune/Inflammatory Response. Feb 2010.
  - Boutzios G, Kaltsas G. Immune system effects on the Endocrine System. March 2015.
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