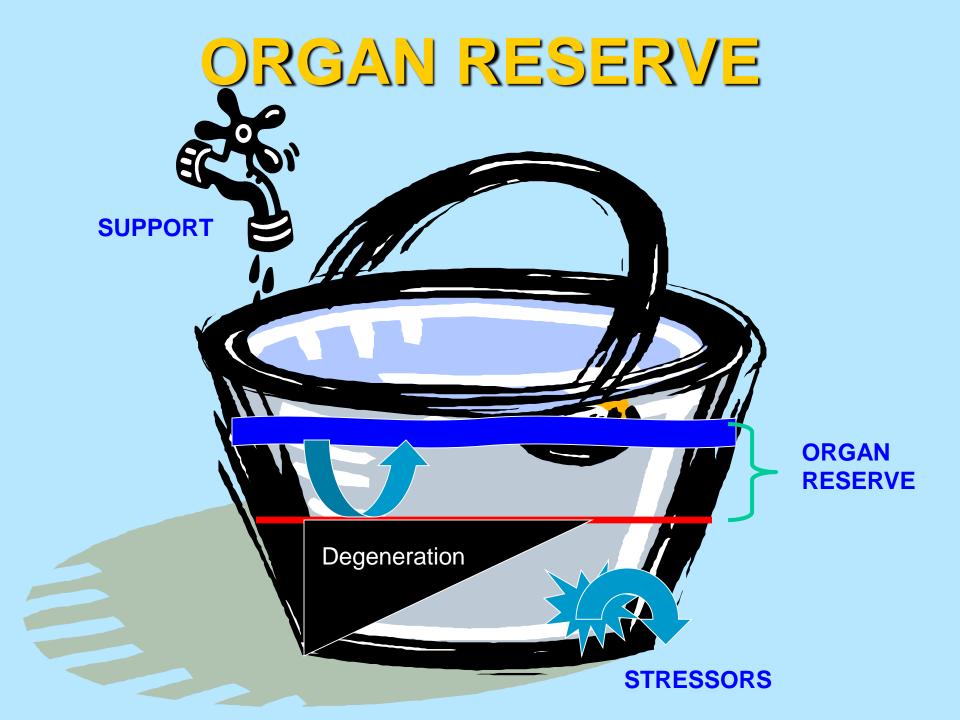
SUBCLINICAL HYPOTHYROID

MANAGING PATIENTS USING RESTING METABOLIC RATE AND BRACHIORADIALIS REFLEXOMETRY

Dr. Konrad Kail 480-905-9200 kkail@cox.net

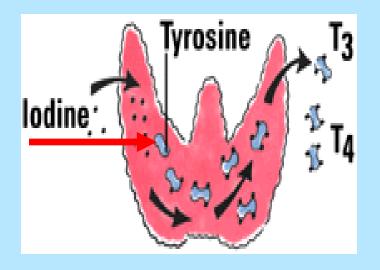
GENERAL CONSIDERATIONS

- MUST WORK FOR HUMANS TO FUNCTION
 - ABSORPTION AND ASSIMILATION
 - DETOXIFICATION AND ELIMINATION
 - **REGULATION**
- STRESS IMPACTS ALL OF THESE BUT THE MOST PROFOUND AND IMMEDIATE EFFECT IS ON REGULATION
 - ADRENAL AND THYROID GLANDS ARE THE MOST STRESS LABILE
- ADRENAL AND THYROID INTERACT IN REGULATING
 - WEIGHT
 - ENERGY
 - BLOOD SUGAR
 - BLOOD FATS
 - NEUROTRANSMITTERS
 - SEX HORMONES
 - INFLAMMATION
 - IMMUNE FUNCTION

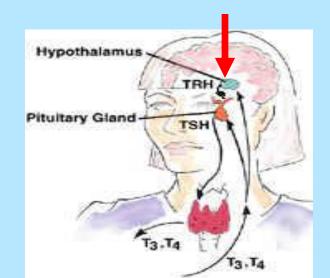


Thyroid Feedback Regulation

The thyroid gland uses **L-Tyrosine** and **lodine** to make T4, the storage form of thyroid hormone and T3 the active form



The production of thyroid hormone is controlled by a feedback loop. When there is not enough receptor site activity in the hypothalamus, TRH is elaborated which stimulates the anterior pituitary to make TSH, which then stimulates the thyroid to make more T3 and T4.



SUBCLINICAL HYPOTHYROID

- SYMPTOMS COMPATIBLE WITH HYPOTHYROID (≥ 12 on Symptom Survey)
- LOW BBT (< 97.5° F axillary)</p>
- SLOW REFLEXES (≥ 137 msecs)
- LOWER RMR
- NORMAL TO SLIGHTLY HIGH TSH
- NORMAL FREE T3, FREE T4
- NORMAL T3U, T4, T7
- PREVALENCE UNKNOWN (8-30%)

CARDIOVASCULAR RISK

INCREASED

- SERUM LIPIDS
- HOMOCYSTEINE-
- C-REACTIVE PROTEIN -
- CORONARY HEART DISEASE
- HYPERTENSION
- ISCHEMIC HEART DISEASE
- ENDOTHELIAL DAMAGE
- COAGUABILITY
- PERIPHERAL ARTERY DISEASE

DECREASED

- STROKE VOLUME
- CARDIAC OUTPUT

MARKERS OF SUDDEN DEATH RISK

DIABETES RISK

- DISRUPTION OF GLP-1 SIGNALLING
- DECREASED THYROID FUNCTION UP TO 18 HOURS AFTER HYPOGLYCEMIC EPISODES
- ASSOCIATED WITH INSULIN RESISTANCE
 INCREASED
- HOMA AND TRIG/HDL
- DYSGLYCEMIA
- OBESITY

ARTHRITIS & INFLAMMATION

- INCREASED RATES OF HASHIMOTO'S
- INCREASED EUTHYROID SICK RISK
- RA PATIENTS WITH SUBCLINICAL HYPOTHYROID HAD DYSFUNCTIONS OF GLUCOSE METABOLISM AND INSULIN RESISTANCE

NEURO-PSYCHOLOGICAL RISK

- **INCREASED**
- HOFFMAN'S SYNDROME
 - WEAKNESS AND STIFFNESS
- DUPUYTREN'S CONTRACTURE
- CARPAL TUNNEL SYNDROME
- POLYMYOSITIS-LIKE SYNDROME
- PARKINSONS
- HEARING LOSS
- ANXIETY AND DEPRESSION
- 1.97 RELATIVE RISK OF COGNITIVE DECLINE (ALZHEIMER'S)

BONE RISK

INCREASED

- BONE RESORPTION IN HYPERTHYROID
 - URINARY PYRIDINOLINE
 - URINARY DEOXYPYRIDINOLINE
 - URINARY CALCIUM
 - SERUM TELOPEPTIDES
- NO CALCIUM METABOLISM PROBLEMS IN HYPOTHYROID
 - CALCIUM BINDS THYROID

(TAKE THYROID AT LEAST 45 MINS AWAY FROM CALCIUM)

PREGNANCY

- FERTILITY ISSUES
- 3 FOLD INCREASE IN PLACENTA PREVIA
- 2 FOLD INCREASE IN PREMATURE DELIVERY
- MAY AFFECT MENTATION IN OFFSPRING
 - NOT WELL STUDIED

FACTORS AFFECTING THYROID FUNCTION

- PERIPHERAL CONVERSION OF T4 TO T3
 - HEPATIC, RENAL, MITOCHONDRIAL FUNCTION
 - DECREASED 5'D-1
 - INHIBITED BY IL-1, IL-6
- TOXIC MATERIALS
 - LEAD, MERCURY
 - PCB
 - FUNGICIDES, ORGANO-CHLORINE INSECTICIDES
- DRUGS
 - AMIODORONE, ANTI-CONVULSANTS, SALSALATE, LITHIUM
- MITOCHONDRIAL PROTEIN LEAKAGE
 - UNCOUPLING PROTEIN 3
- CYTOKINES
 - NF-KAPPA-B
 - TNF-ALPHA
 - IL-1 ALPHA/BETA
- EUTHYROID SICK SYNDROME IMPAIRS FUNCTION UP TO 60 DAYS FOLLOWING ACUTE SEVERE ILLNESS

DISTRIBUTION OF THYROID

Organ Distribution of T₃ and T₄

In humans, the extra thyroidal pool of T_3 and T_4 is distributed as follows:

Table

Organ	T ₄	T ₃
Liver & Kidney	33%	5-7%
Skin, muscle, brain	44%	75%
Plasma	22%	18%

DECREASED CONVERSION

- Peripheral conversion of $T_4 \rightarrow T_3$ is reduced by:
- 1. Carbohydrate intake restriction
- 2. Chronic illness
- 3. Hypothyroidism
- 4. Increased glucocorticoids-or high stress states
- 5. Estrogens
- 6. Deficits in tissue cofactors
- 7. *B*-Blockers

REVERSE T3 (RT3)

	T ₄	T ₃	rT ₃	Remarks
mean serum concentration ng/ml	80	1.4	.25	serum T_4 is 60x more abundant than T_3
body distribution	10	38	90	T ₄ is mostly confined
volume (L)				to vascular space
production rates	88	30	28	T ₃ distributes in vascular
mg/day				and ECF space
% derived	-	>80	>95	rT ₃ distributes
from T ₄				in total body

The ratio in the gland of $T_4/T_3 = 10$

Vasoactive Intestinal Peptide and Thyroid Function

VIP exerts action through 2 receptors VPAC1 and VPAC2

- VPAC1 receptors are in liver, breast, kidney, prostate, ureter, bladder, pancreatic ducts, GI mucosa, lung, thyroid, adipose tissue, lymphoid tissue, and adrenal medulla.
- VPAC2 receptors are in blood vessels, smooth muscles, the basal part of mucosal epithelium in colon, lung, and vasculature of kidney, adrenal medulla and retina. Also present in thyroid follicular cells and acinar cells of the pancreas.
- In hypothyroid, there was a 2-fold increase in all peptides derived from VIP, found in the gastric fundus
- In hypothyroid significant increases of pituitary VIP
- VIP modulates T3 and T4 (decreases) in any inflammation

DE-IODINASES

Bianco AC, Salvatore D, et al. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002 Feb;23(1):38-89.

Туре	Tissues	Site	Substrate Preference	Inhibitors
D1	Liver, Kidneys, Thyroid	Plasma membra	rT3, T4, T3	PTU, T4+, IL1, IL6,
	T4 t	o T3 CON	ΤΝϜα	
D2	Thyrotrophs, Hypothalamus,	Endo. Retic	T4, rT3	lopanoate, T4+, T3+
Skeletal Muscle, Heart, Thyroid		CTION ON		
D3	Brain, Placenta, Pregnant Uterus, Skin	Sub Plasma Memb	T3, T4	lopanoate, Dexamethas one

Thyroid Receptor Phenotypes

Alkemade A, Vujist CL, et al. Thyroid hormone receptor expression in the human hypothalamus and anterior pituitary. J Clin Endocrinol Metab. 2005 Feb;90(2):904-12.

TYPE	TISSUES
ΤRβ2	Pituitary Thyrotrophs
ΤRβ1	Liver, Kidney T4 to T3 Conversion
TRα1	Skin, Muscle, Heart Brown Fat
TRα2	Brain Action on Metabolism Hypothalamus (inhibitory)

TSH- REGULATION MAY NOT REPRESENT METABOLIC DEMAND

TISSUE	ACTION	RECEPTOR	DE-IODINASE
HYPOTHALAMUS BRAIN (action on metabolism)	TRH	TR-α2	D2, D3
THYROTROPHS (Pituitary)	TSH	TR-β2	D2
THYROID (T4, T3 production)	T4, T3	TR-β2 ?	D1, D2
LIVER KIDNEYS (T4 to T3 conversion)	Т3	TR-β1	D1
SKELETAL MUSCLES HEART		TR-α1	D2

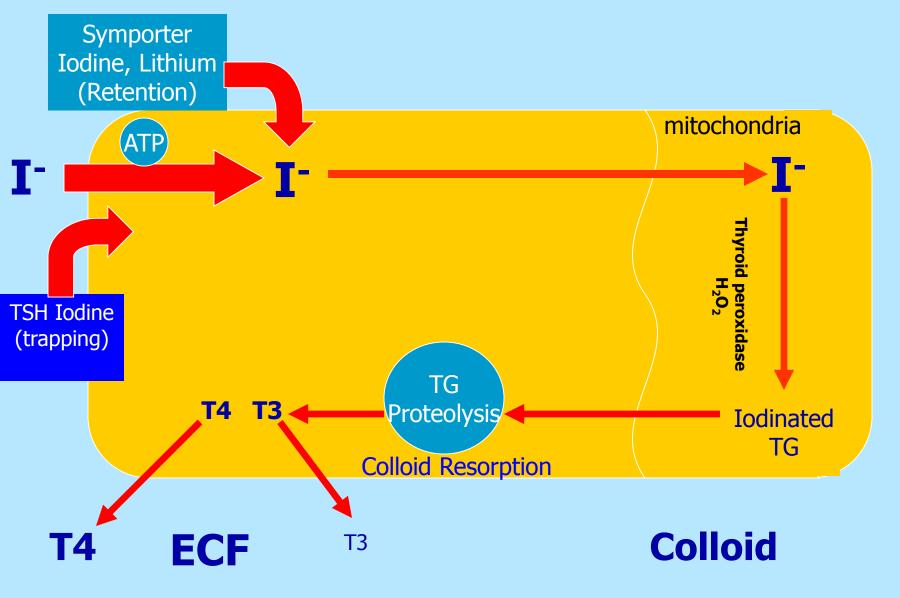
NUTRIENTS AND THYROID

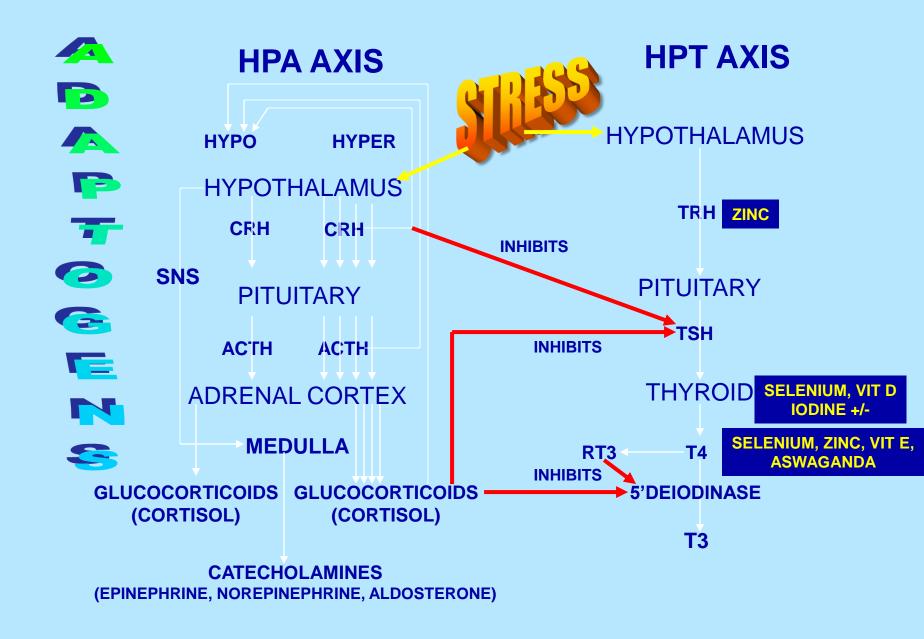
- SELENIUM
 - IMPROVES FUNCTION DECREASES RECOVERY TIME IN EUTHYROID SICK SYNDROME
- IRON AND ZINC
 - INCREASE THYROID FUNCTION IN IRON/ZINC DEFICIENT
 - NO EFFECT IN IRON/ZINC SUFFICIENT
- CALCIUM
 - INHIBITS ABSORPTION
- ALPHA-TOCOPHEROL
 - NO EFFECT
- KELP AND ALL IODINE
 - HELPFUL IN IODINE DEFICIENT
 - DOSE DEPENDENT DECREASE IN THYROID FUNCTION IF IODINE SUFFICIENT
- L-CARNITINE DECREASES THYROID FUNCTION
 - PREVENTS THYROID HORMONE ENTRY INTO NUCLEUS OF CELLS
- High Soy intake inhibits thyroid function
 - Ipriflavone helps bone resorption but does not increase cancer risk

Lithium and Thyroid Function

- Enters thyrocyte via the Na⁺/I⁻ Symporter
- Concentrated in thyroid gland to 3-4 times serum levels
- Increases intra-thyroidal iodine content
- Inhibits coupling of iodotyrosine residues
- Decreases colloid droplet formation
- Inhibits microtubule formation
- Inhibits thyroid hormone secretion
- Blocks iodine release from thyroid gland
- Treats hyperthyroid in people allergic to iodine

lodine Uptake and Retention





Hypercortisolemia Inhibits Thyroid Function

Influence of Other Hormones on Thyroid Activity

STRONG THYROID STIMULATORS	MILD THYROID STIMULATORS	STRONG THYROID INHIBITORS	MILD THYROID INHIBITORS
Growth Hormone IGF-1 Testosterone Other Androgens	DHEA Androstenedione Melatonin Progesterone Cortisol at physiologic doses	ORAL ESTROGENS OF ANY TYPE	Transdermal or injectable Estradiol, Cortisol in small doses
Insulin In patients with insulin deficiency	Erythropoietin (hypothetical)	Cortisol and other Glucocorticoids at	Insulin In patients
É H	ERTOGHE, T; The Ho landbook. Internation urrey, UK, 2006, p88.	with insulin resistance	

Hypothyroid Causes Adrenal Dysfunction

- Results in hypersecretion of CRH and AVP from hypothalamus
- Significantly increased pituitary content of VIP
- Adrenal weight,

 Corticosterone
- ACTH, CRH, AVP

Tohei A. Studies on the functional relationship between thyroid, adrenal and gonadal hormones. J Reprod Dev 2004 Feb;50(1):9-20.

MEASUREMENTS OF THYROID FUNCTION

SERUM MEASUREMENTS

- What's on the shelves at the pharmacy
- TSH INSENSITIVE WHEN APPROACHING NORMAL
- PHYSIOLOGIC MEASUREMENTS
 - What you took home from the pharmacy
- BODY MASS INDEX
 - CORRELATION WITH RESTING METABOLIC RATE
- BASAL BODY TEMPERATURES
 - IDENTIFY SUBCLINICAL HYPOTHYROID
 - TOO SLOW TO RESPOND TO TREATMENT
- RESTING METABOLIC RATE
 - SOME ARTIFACTS
 - CONGESTION
 - REACTIVE AIRWAY DISEASE
 - ASTHMA OR OTHER COPD
- REFLEXES
 - ACHILLES, BRACHIORADIALIS, STAPEDIAL
 - NO ARTIFACTS UNLESS NERVE DAMAGE

METHODOLOGY

- ENTRY CRITERIA
 - BBT<97.5° F AXILLARY AVERAGE (BRODA BARNES)
- BASELINE MEASUREMENT AND THIRTY DAY TREATMENT INTERVALS
 - SYMPTOM SURVEY
 - BODY MASS INDEX
 - **RESTING METABOLIC RATE (oxygen consumption)**
 - BRACHIORADIALIS REFLEXOMETRY (mean of 4)
 - TSH,T3U, T4, T7
 - ADDED FREE T3, FREE T4
 - SOME HAD
 - MICROSOMAL (TPO) AB
 - THYROGLOBULIN AB
 - REVERSE T3
 - THYROTROPIN RELEASING HORMONE
 - LIPIDS
 - CHOLESTEROL
 - LDL
 - HDL
 - TRIGLYCERIDES

RESTING METABOLIC RATE MEASUREMENT VIA OXYGEN CONSUMPTION

50



PROTO-TYPE BRACHIORADIALIS REFLEXOMETRY SYSTEM

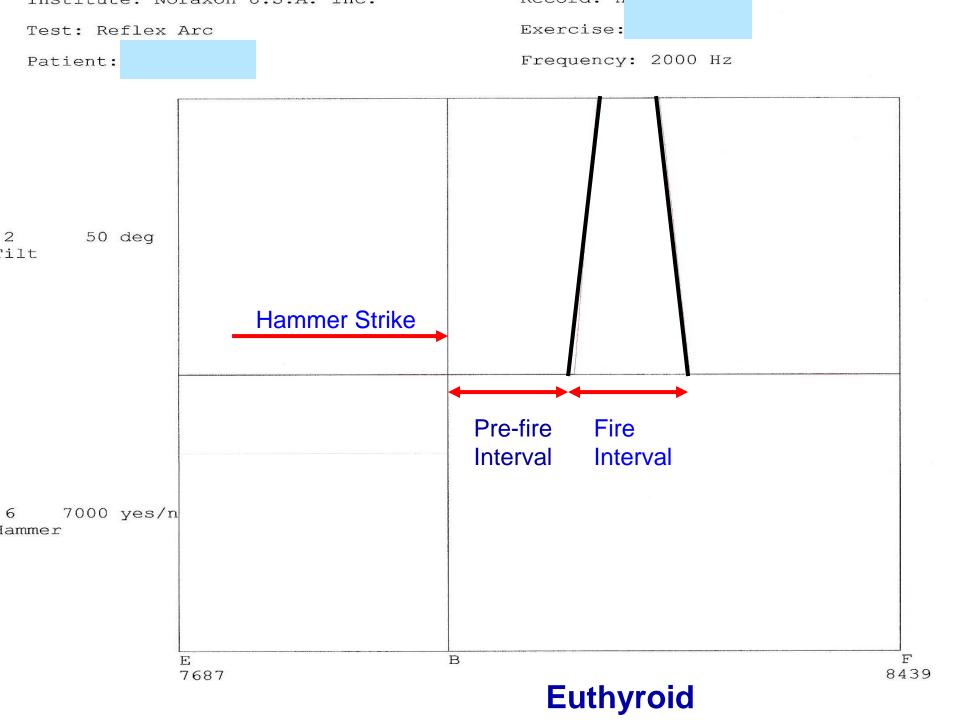


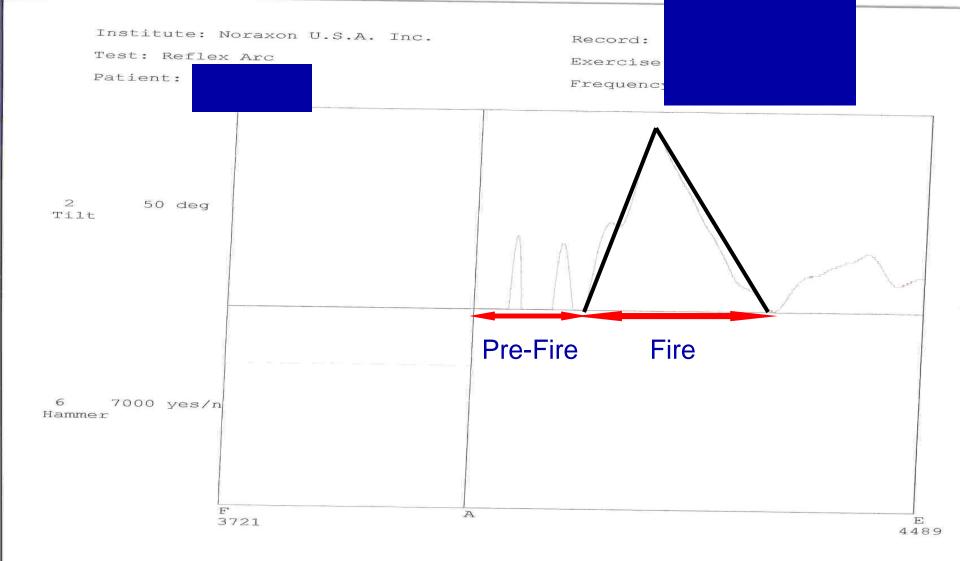


Link

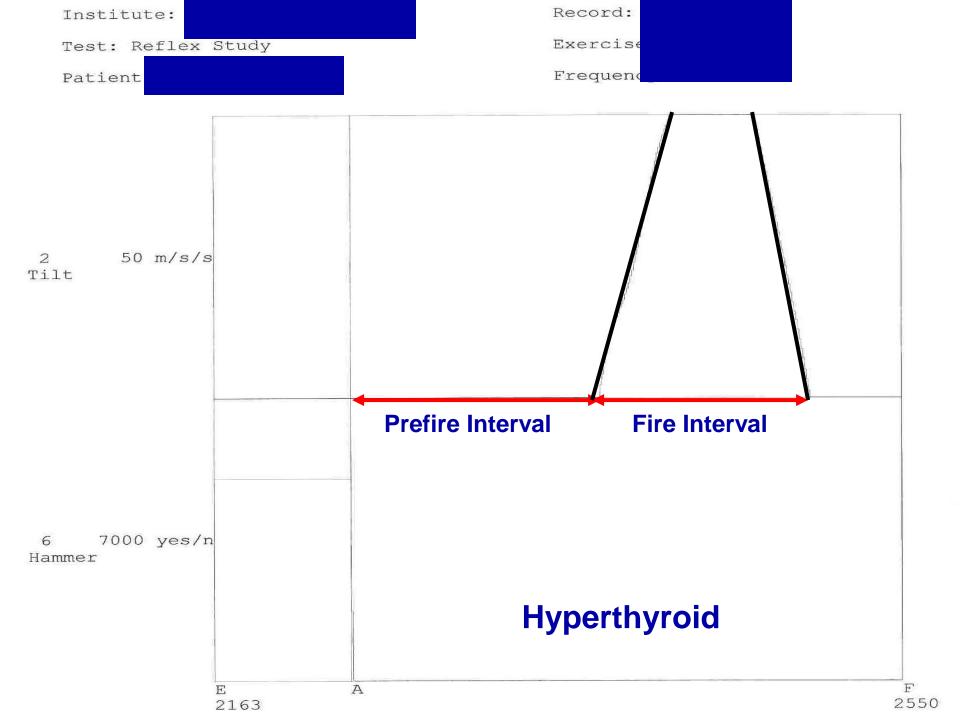
Hammer

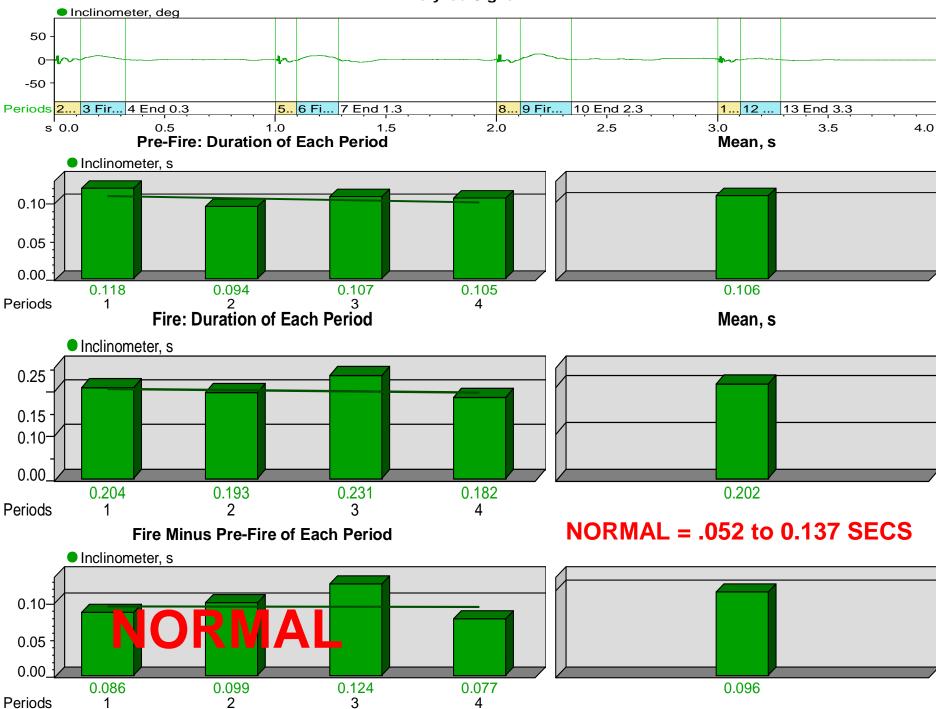




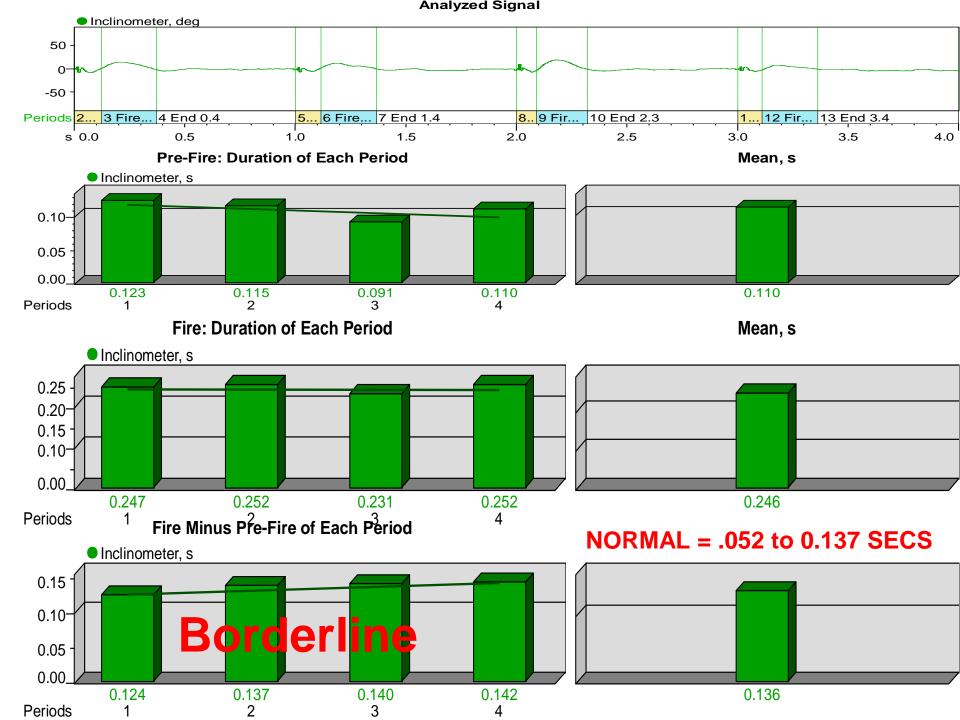


HYPOTHYROID





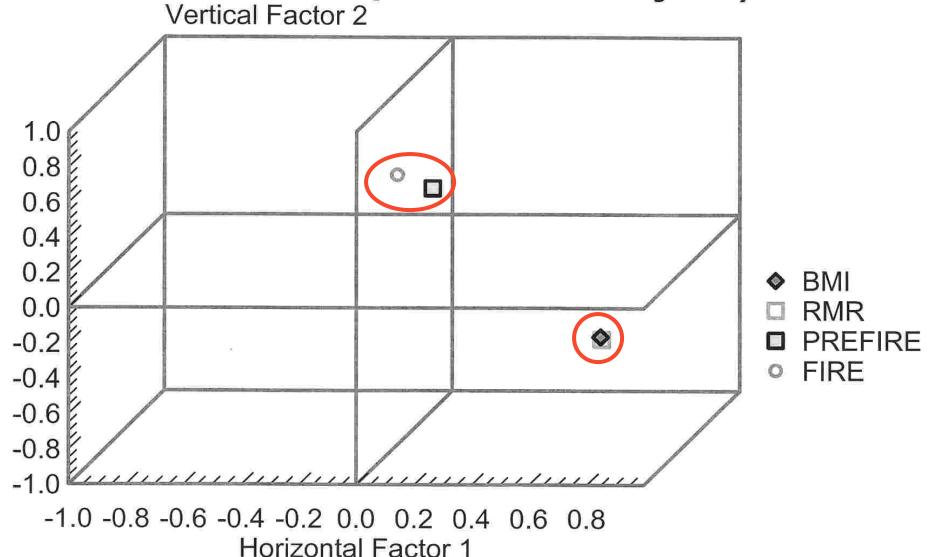
Analyzed Signal



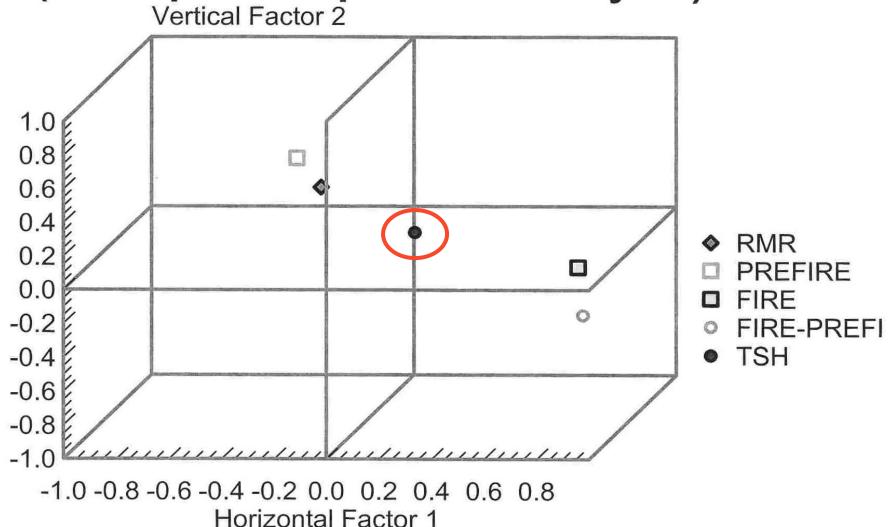
Histogram of Unselected Cases Dependent Variable: RMR 60 50. 40 30 20 Frequency Std. Dev = .92 10 Mean = -.40 N = 468.000 8 8 8 8 8 8 8 13 13 13 13 5. 8.

Regression Standardized Residual

Factor Loadings - Unrotated Solution (Principal Components Analysis)



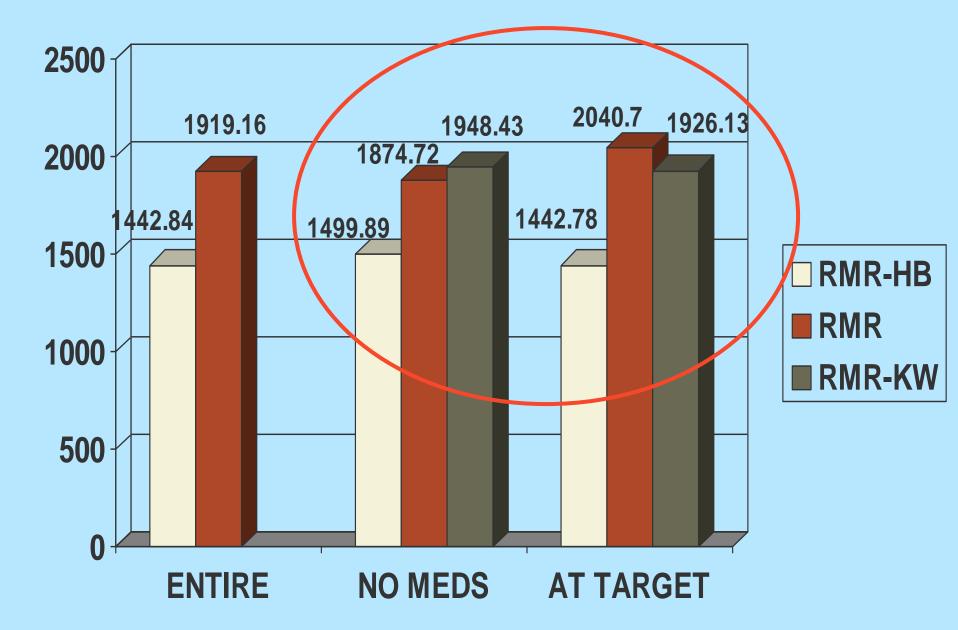
Factor Loadings - Unrotated Solution (Principal Components Analysis)



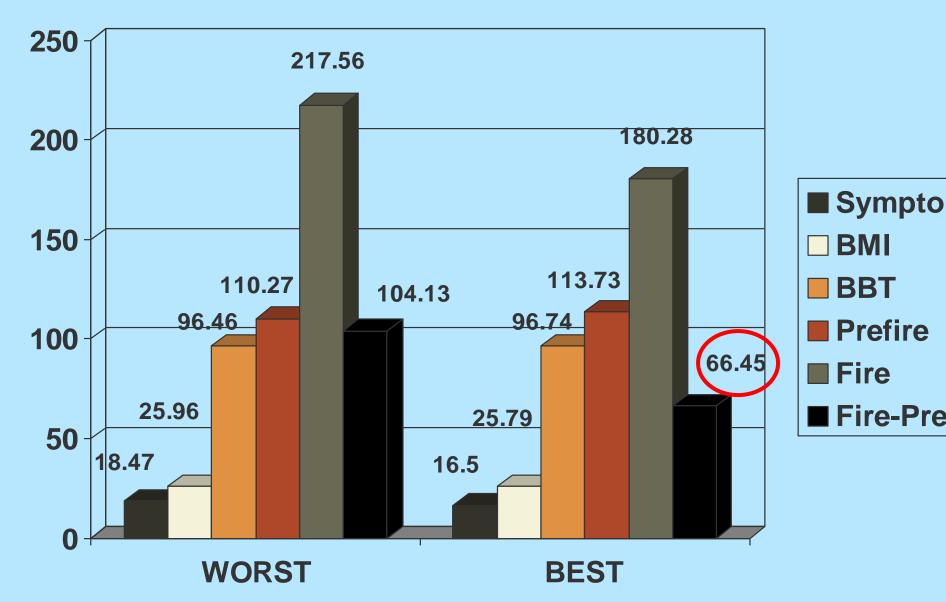
KAIL-WATERS EQUATION

RMR = 2307.62 + [-7.53(CM)] + [27.09(KG)] + [-42.59(BMI)] + [-45.47(PREFIRE)] + [45.85(FIRE)] + [-46.27(FIRE-PREFIRE)]

PREDICTED vs MEASURED RMR



WORST TO BEST 1st Cohort

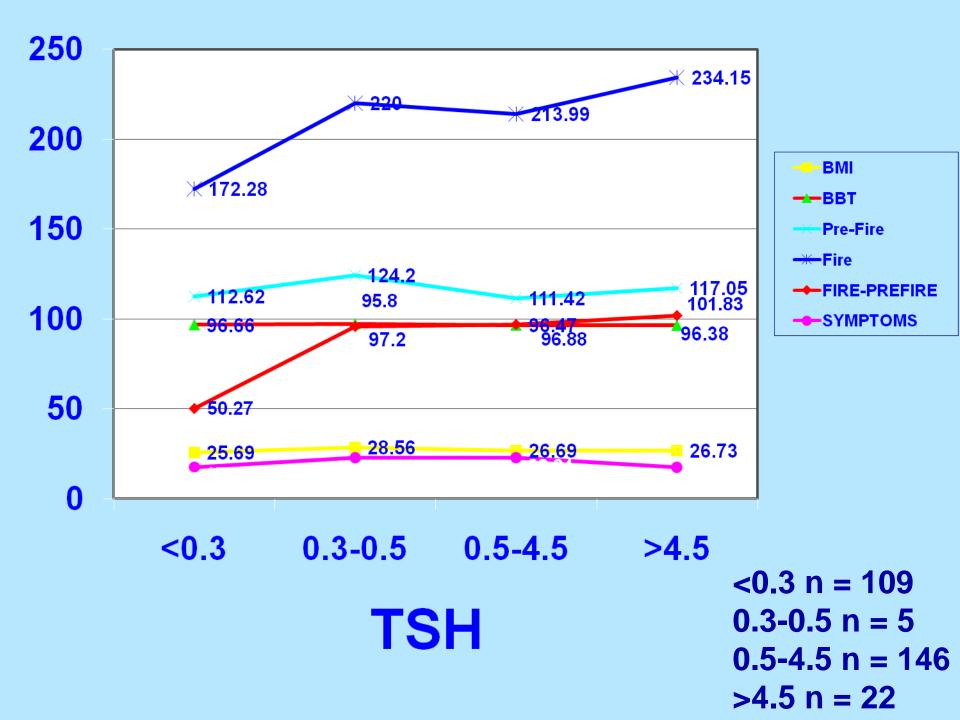


WHY TSH DOES NOT IDENTIFY THOSE AT RISK !!!

TSH gets too low before adequate effect (TRMR)



TSH <0.3 FIRE-PREFIRE<66



PREDICTABILITY OF BRACHIORADIALIS REFLEX TESTING

179 in Subpopulation on No Medication	Normals	Hypothyroid (+)	Euthyroid (-)
Resting Metabolic Rate	\geq 2000 kcals.	117	58
Brachio- Radialis Reflex	Fire-Prefire ≤ 66 msecs.	123	57

PREDICTABILITY OF BRACHIORADIALIS REFLEX TESTING

	Gold Standard RMR (+)	Gold Standard RMR (-)
BR Test (+)	True Positives (117)	False Positives (6)
BR Test (-)	False Negatives (1)	True Negatives (58)

SENSITIVITY

Sensitivity is the proportion of those that are hypothyroid that are correctly diagnosed. It is expressed as:

<u>True Positives</u> = <u>117</u> = 0.992 True Positives + False Negatives 117 + 1

SPECIFICITY

Specificity is the proportion of those that are euthyroid that were correctly identified. It is expressed as:

<u>True Negatives</u> = <u>58</u> = 0.906 True Negatives + False Positives 58 + 6

PREDICTIVE VALUE of POSITIVE TEST

Predictive Value of a Positive Test is the proportion of those with a positive test that are hypothyroid.

It is expressed as:

<u>True Positives</u>	=	<u>117</u> _= 0.951
True positives + False Positives		117+6

PREDICTIVE VALUE of NEGATIVE TEST

Predictive Value of a Negative Test is considered the proportion of those with a negative test who are euthyroid:

It is expressed as:

True Negatives	= _	<u>58</u>	_= 0.983
False Negatives + True Negative	es	1 + 58	

HOW TO OPTIMIZE THYROID ACTIVITY AND TREATMENT

	WHAT TO DO	WHAT TO AVOID
DIET	1500-2500 CAL/DAY ORGANIC PALEOLITHIC FOODS IRON RICH FOODS HERTOGHE, T; The Hormone Handbook. International Medical Books Surrey, UK, 2006, p87.	LOW CALORIE, LOW FAT DIETS SKIPPING MEALS INDUSTRIALIZED FOODS ALCOHOL, VINEGAR CAFFEINE EXCESS ANIMAL PROTEIN FIBER RICH CEREALS
SLEEP	SLEEP SUFFICIENTLY 6-9 HRS/NIGHT	SLEEP DEPRIVATION
STRESS	SOME STRESS MANAGEMENT TECHNIQUE	PROLONGED STRESS EXCESSIVE PHYSICAL ACTIVITY

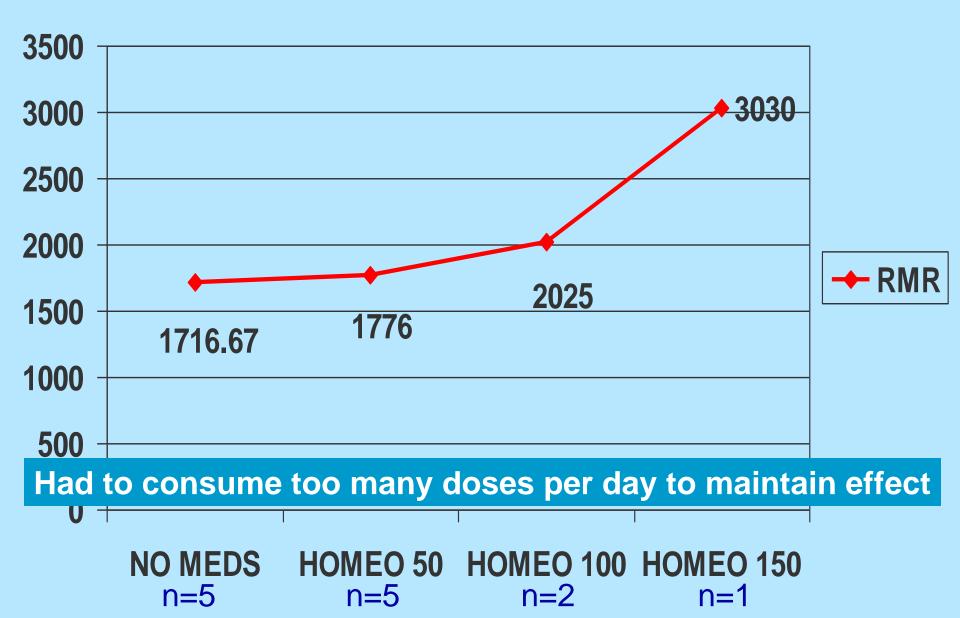
OTC THYROID AGENTS AGENT CONTENTS

HOMEOPATHIC THYROID STIMULATOR	THYROID 5C, NATIVE GOLD 8X, BLACK CURRANT BUDS 1DH, BLOODTWIG DOGBERRY BUDS 1 DH, SWEET ALMOND BUDS 1DH, ETHANOL, GLYCERIN, WATER
OTC THYROID TISSUE	NEW ZEALAND SHEEP THYROID TISSUE, RICE POWDER, DI- CALCIUM PHOSPHATE, GELATIN

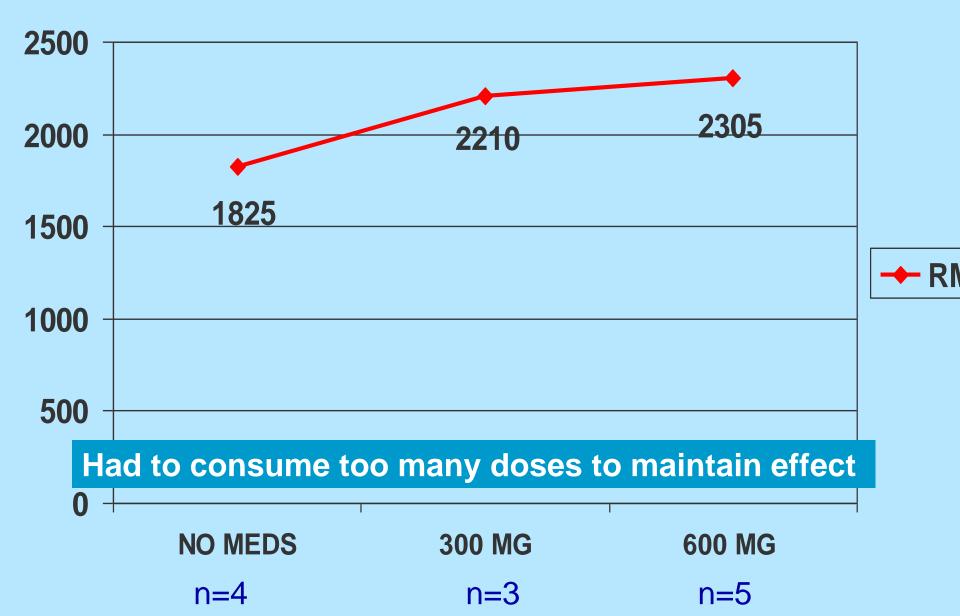
OTC THYROID TISSUE PLUS CO-FACTORS

NEW ZEALAND BOVINE THYROID, L-TYROSINE, ANTERIOR PITUITARY, L-ASPARTIC ACID, IRIS VERSICOLOR, KELP

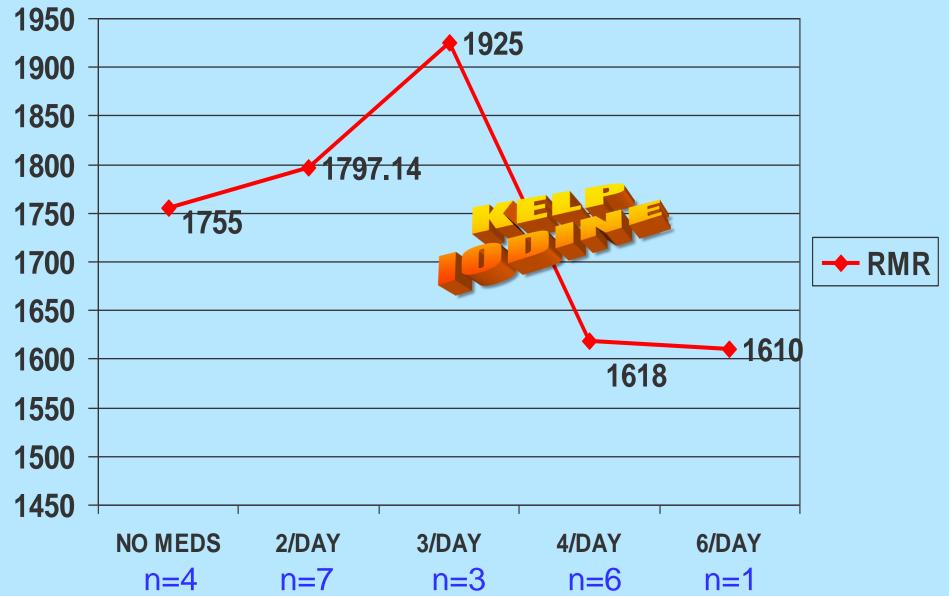
HOMEO AND RMR



OTC THYROID AND RMR



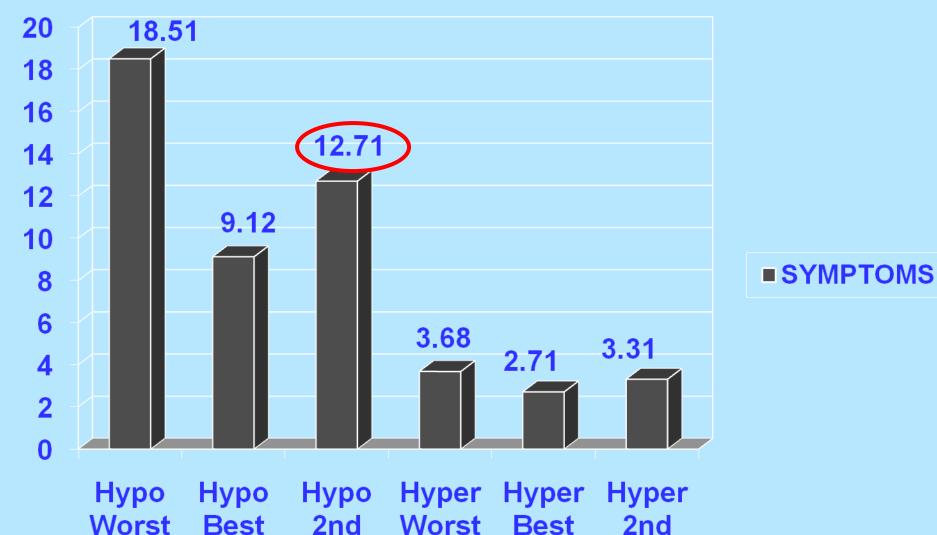
TISSUE AND COFACTORS AND RMR



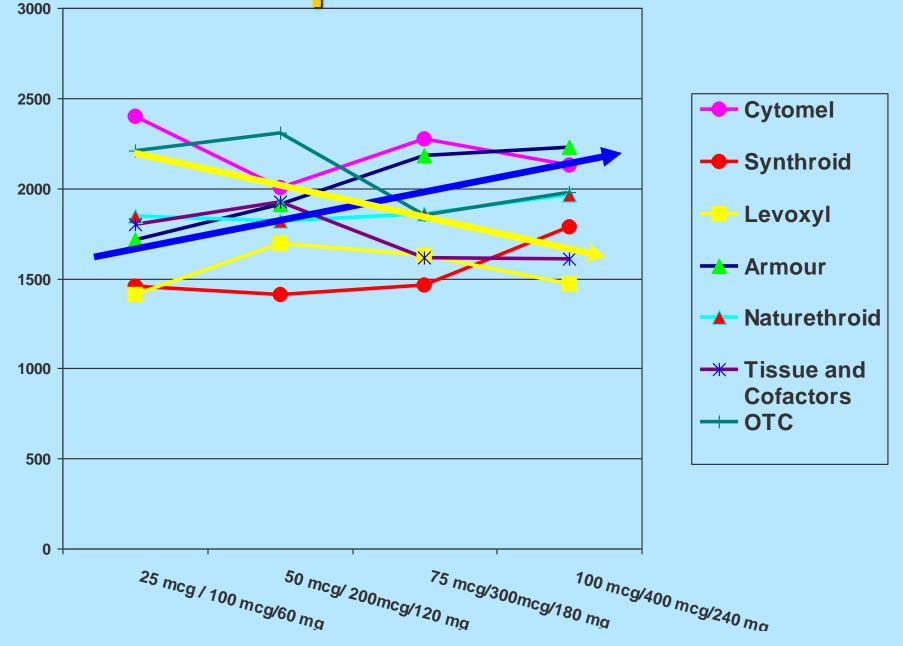
RX THYROID PREPARATIONS

AGENT	EQUIVALENT DOSE	½ LIFE	ADDITIVES	
CYTOMEL	25 MCG	1.4 DAYS	CALCIUM SULFITE, GELATIN, STARCH, STEARIC ACID, SUCROSE, TALC	
SYNTHROID	0.1 MG	6-7 DAYS	ACACIA, SUGAR, CORN STARCH, LACTOSE, MAGNESIUM STEARATE, POVIDONE, TALC	
DESSICATED 38 mcg T4 9 mcg T3	1 GRAIN 60 MG	3-7 DAYS	CALCIUM STEARATE, DEXTROSE, MICROCRYSTALLINE CELLULOSE, SODIUM STARCH GLYCOLATE, OPODY WHITE	

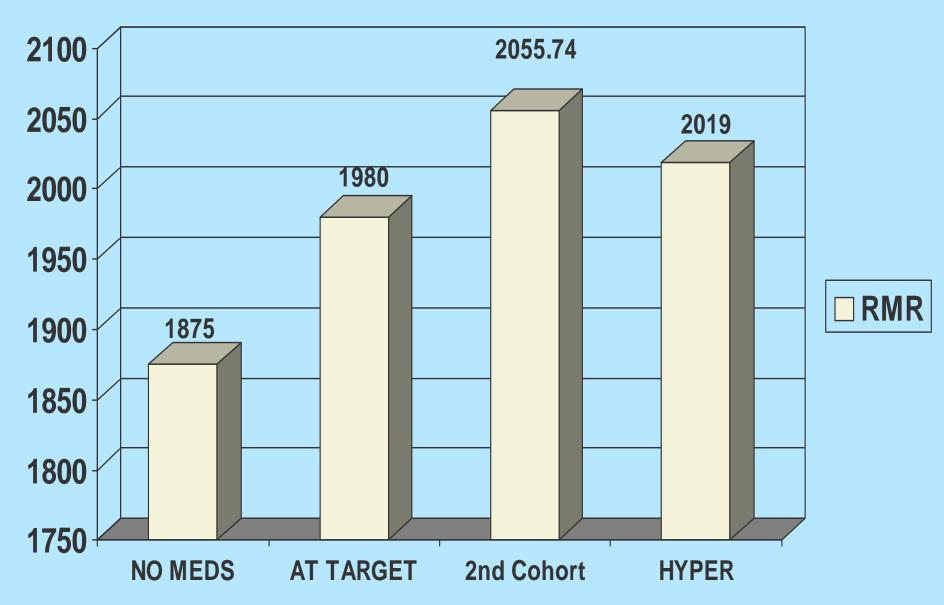
SYMPTOM SCORE WORST TO BEST



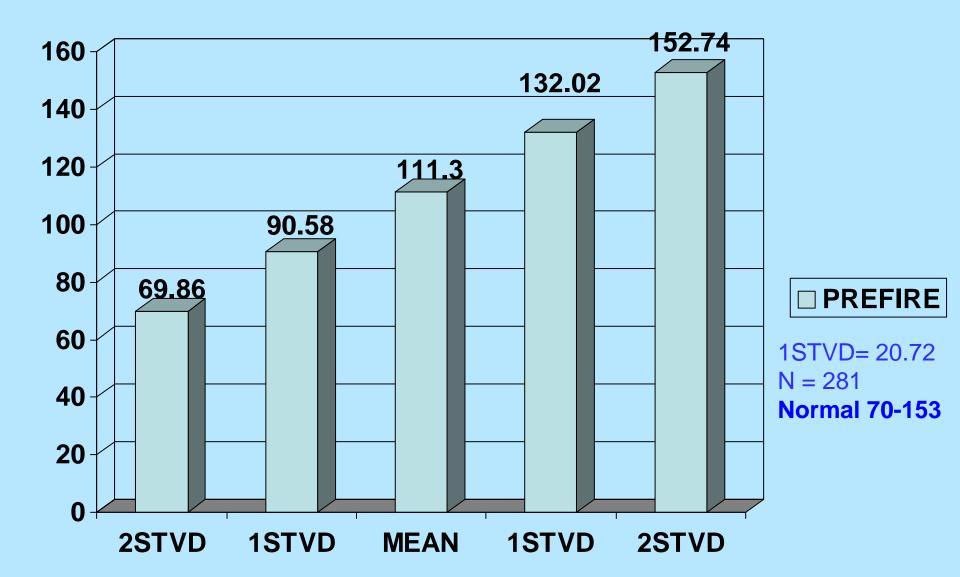
RMR Response to Medication





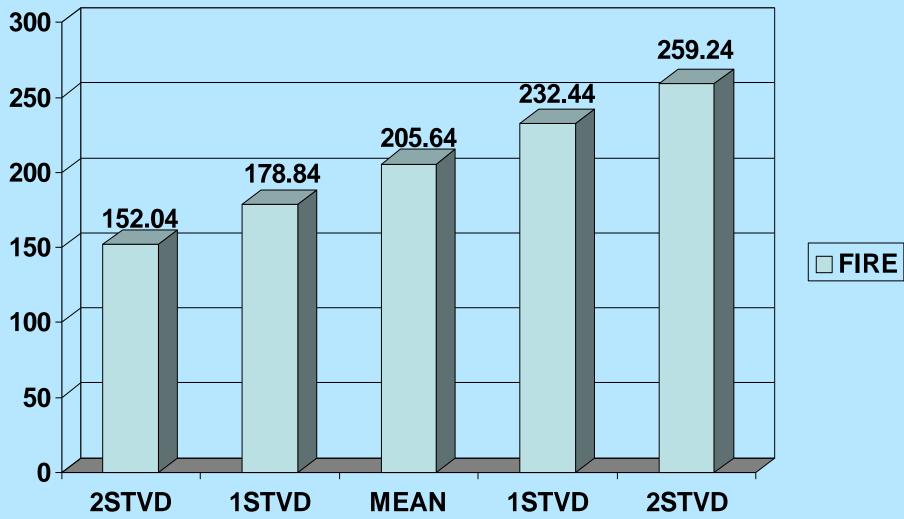


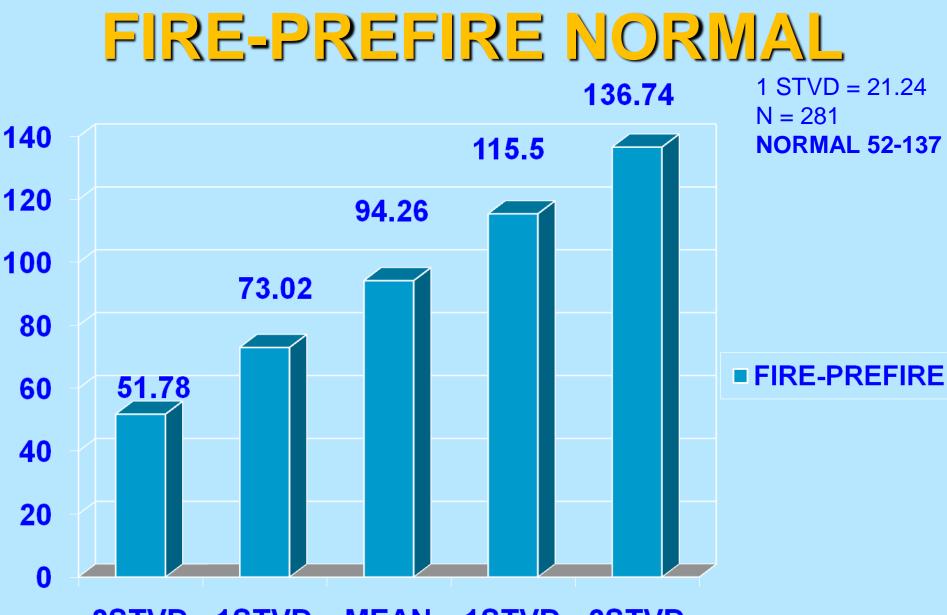
PREFIRE NORMAL



FIRE NORMAL

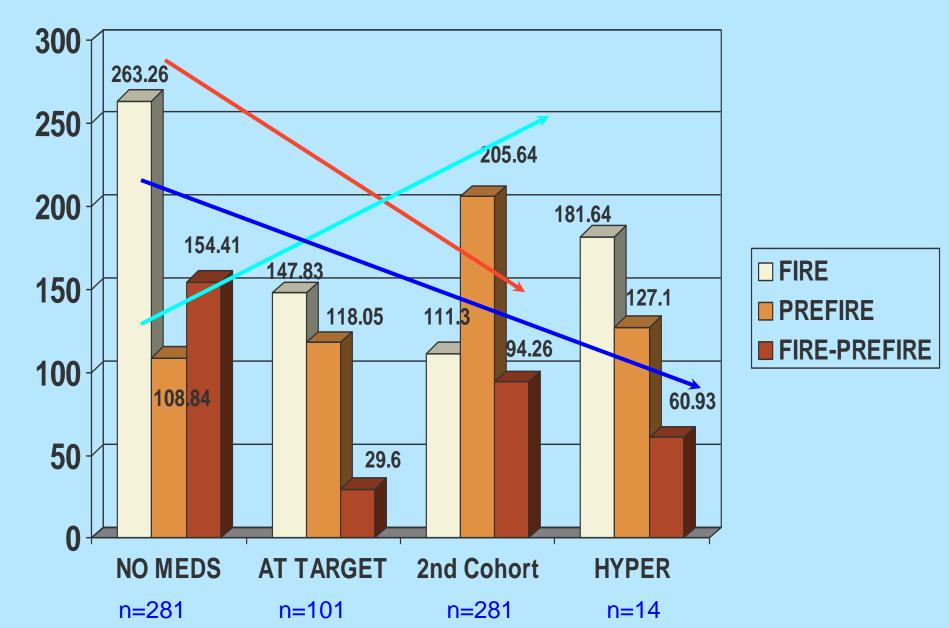
1 STVD = 26.80 N = 281 NORMAL 152-259





2STVD 1STVD MEAN 1STVD 2STVD

REFLEX PARAMETERS



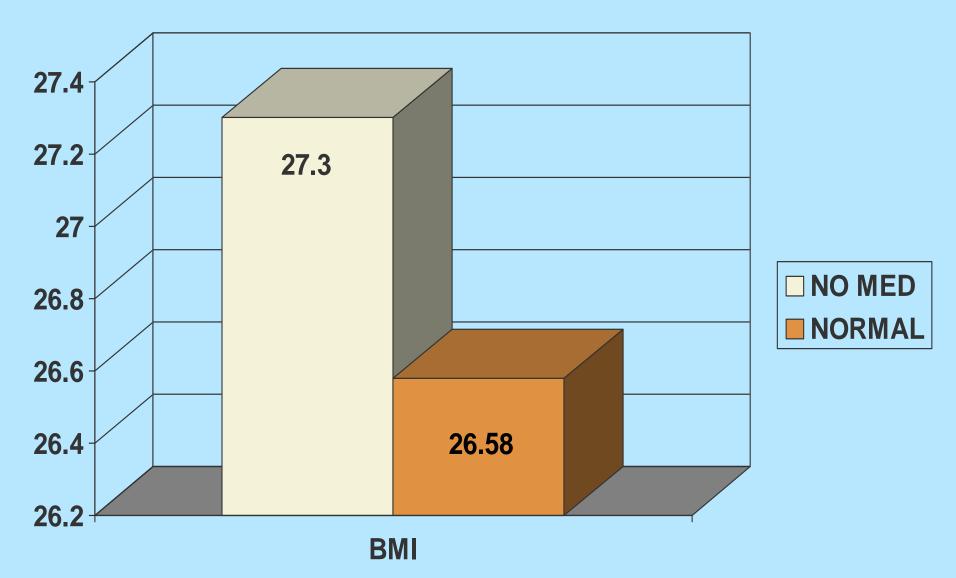
CHANGE IN BBT 2nd Cohort



CHANGE IN WEIGHT 2nd Cohort



CHANGE IN BMI 2nd Cohort



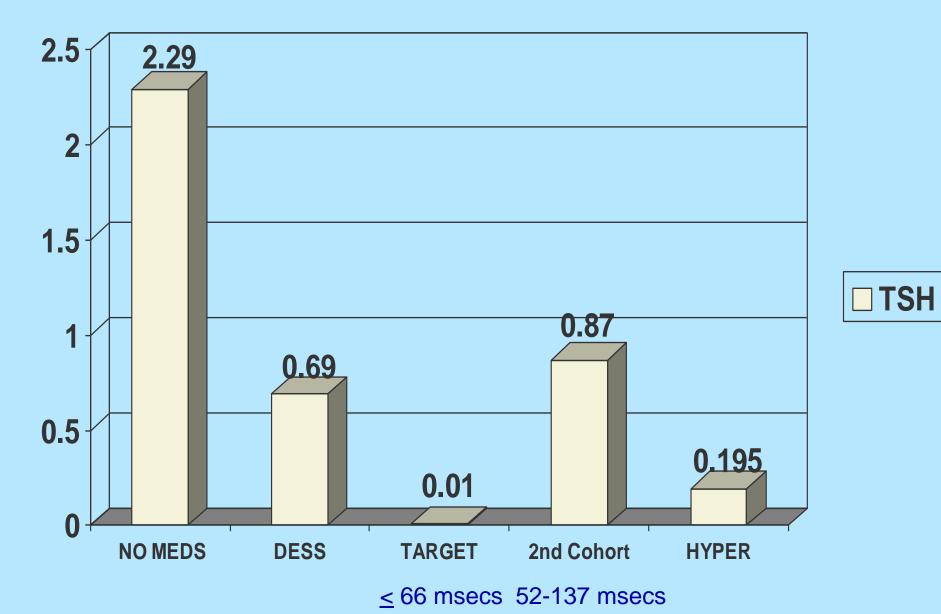
HYPERTHYROID SIGNS

- PALPITATIONS 6:815 0.7% TACHYCARDIA 4:815 2:815 SHAKEY/HYPER HAIR LOSS 1:815 HYPERTENSION 1:815 TOTAL 14:815
 - 0.4% 0.2% 0.1% 0.1%
 - 1.7%

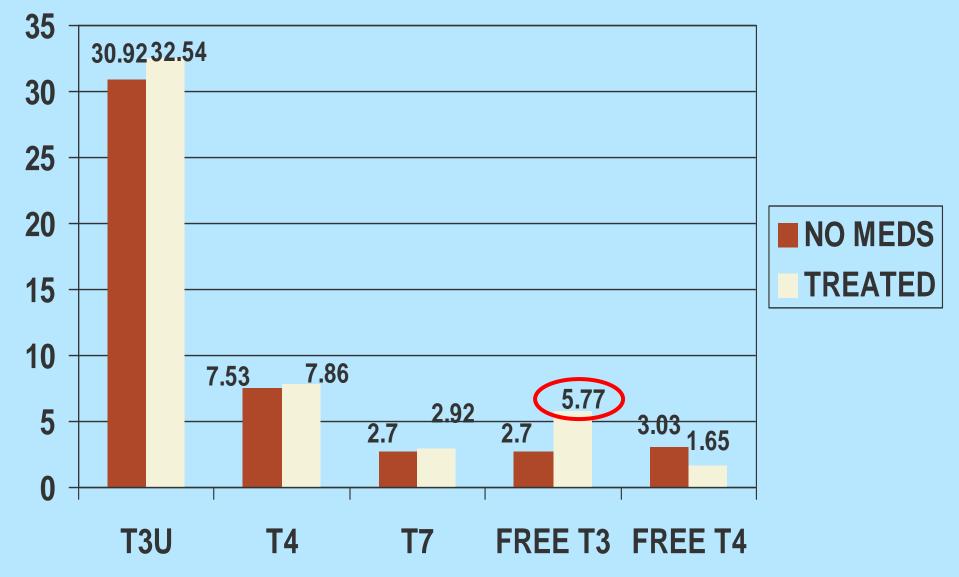
SONORA QUEST NORMALS

TEST	LOW END NORMAL	HIGH END NORMAL
TSH	0.45	4.5
T3U	23.4	42.7
Τ4	4.5	12.5
T7	1.2	4.3
FREE T3	1.8	5.4
FREE T4	0.8	1.9





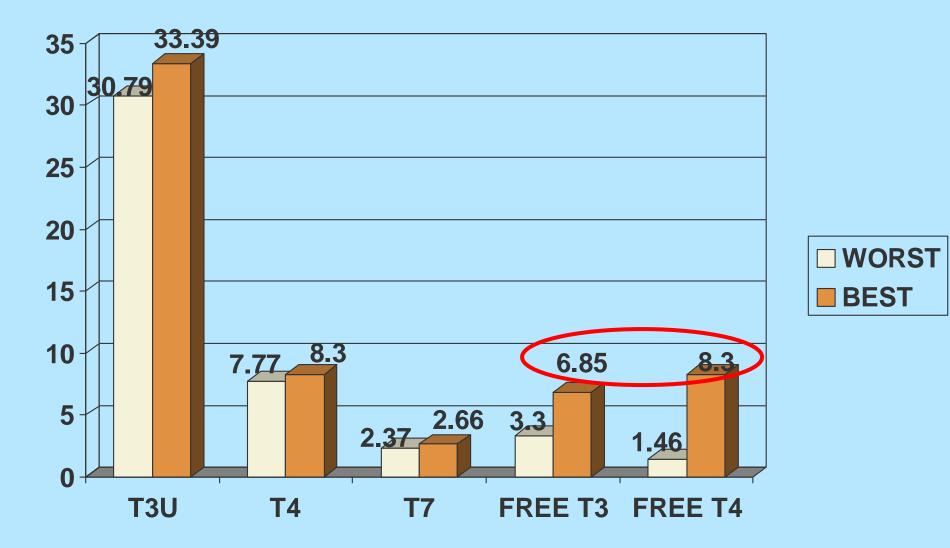
AT TARGET (FIRE-PREFIRE<66)



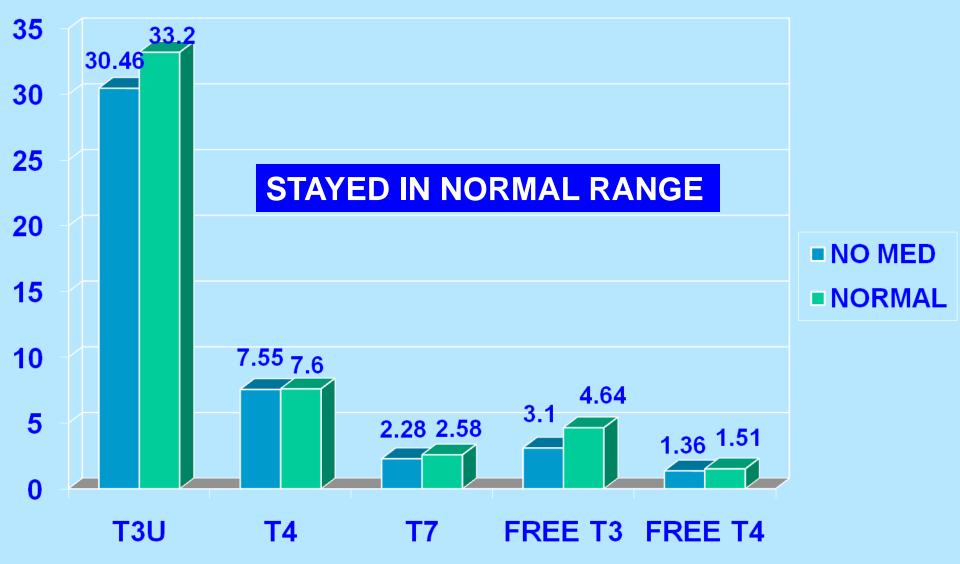
AT TARGET (RMR CHANGE > 355)



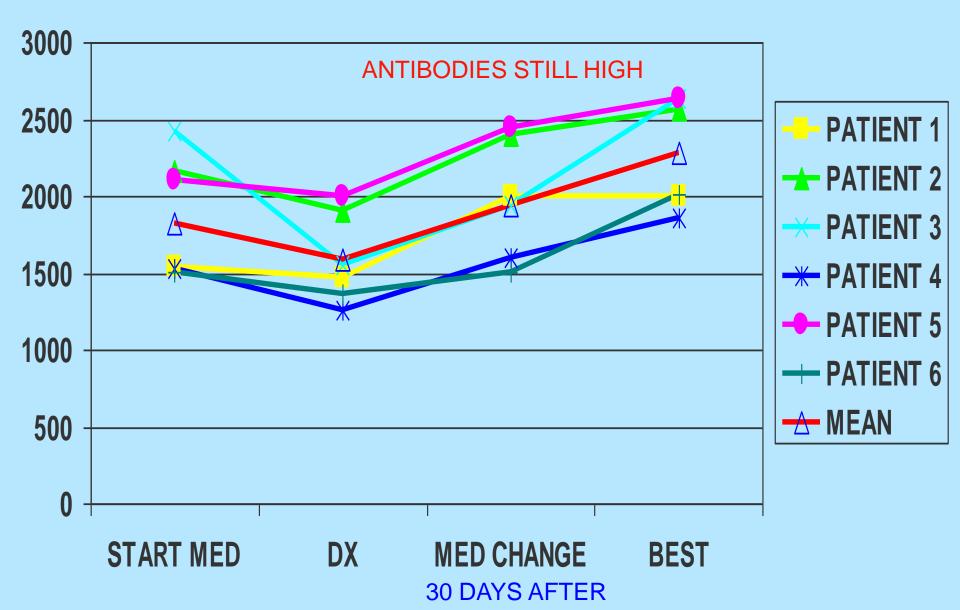
DESSICATED THYROID AND SERUM THYROID HORMONES



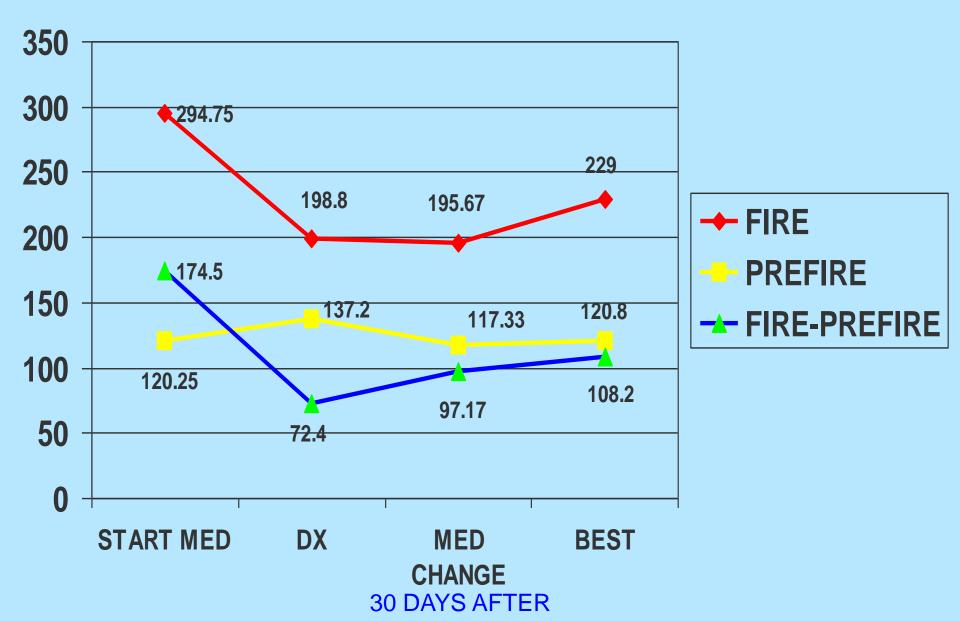
CHANGE IN SERUM HORMONES 2nd Cohort



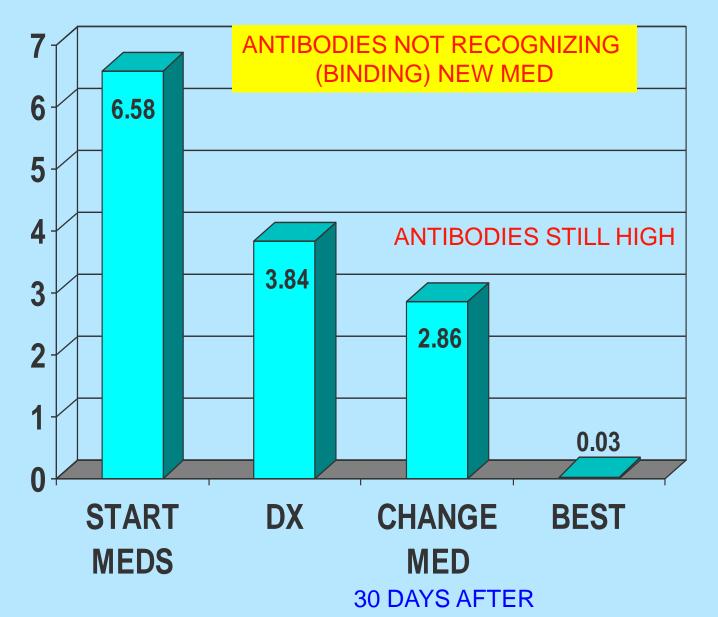
HASHIMOTO'S AND RMR



REFLEXES AND HASHIMOTO'S

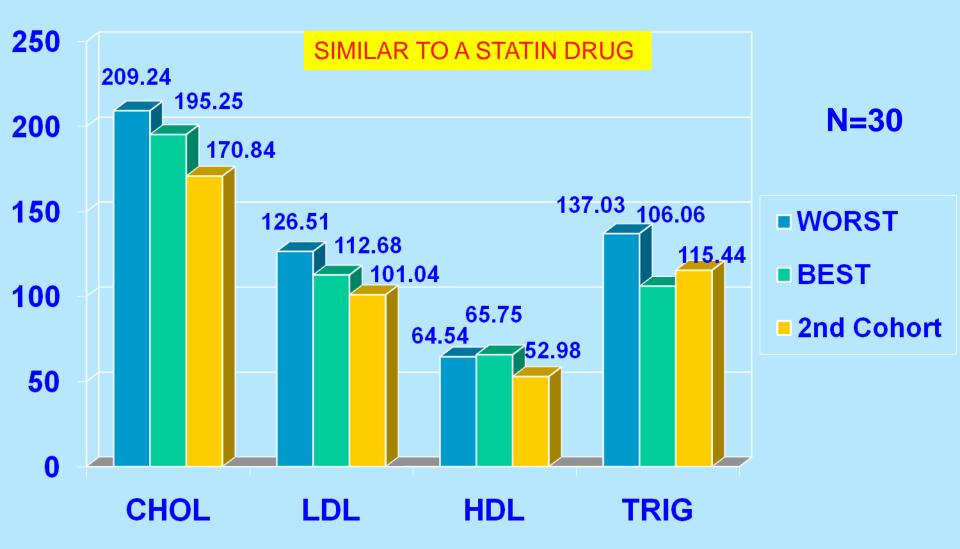


HASHIMOTO'S AND TSH





THYROID EFFECTS ON SERUM LIPIDS



ADAPTING THYROID DOSE TO ENVIRONMENT

DOSE	INCREASE DOSE (5-20% MORE)	LOWER DOSE (5-20% LESS)
CONDITIONS	INSUFFICIENT EFFECTS WINTER IN THE MOUNTAINS EXERCISING A LOT	EXCESSIVE EFFECTS SUMMER AT THE BEACH EXCESSIVE STRESS
HERTOGHE, T; The Hormone Handbook. International Medical Books Surrey, UK, 2006, p89.	HIGH PROTEIN DIET LOW VEGGIE/FRUIT DIET LOW CALORIE DIET BETA BLOCKERS ORAL ESTROGEN SLEEP DEPRIVATION SITUATIONS REQUIRING MENTAL ALERTNESS	LOW PROTEIN DIET HIGH VEGGIE/FRUIT DIET CAFFEINATED DRINKS UNTREATED CORTISOL DEFICIENCY ANDROGENS IN WOMEN GROWTH HORMONE TREATMENT INSULIN TREATMENT

COST OF THYROID MEDS

PHARMACY 30 day supply	ARMOUR 120 mg	SYNTHROID 200 mcg	CYTOMEL 50 mcg
WALGREENS	\$13.79	\$28.19	\$46.49
OSCO	\$21.69	\$39.00	\$75.00
K-MART	\$15.97	\$29.69	\$48.97
COSTCO	\$10.19	\$21.17	\$41.89
AVERAGE	\$15.41	\$29.51	\$53.09

Many on synthetic thyroid require both T3 and T4 Combination Therapy \$82.60 for 30 day supply

THYROID MYTHS does subclincal hypothyroid need to be treated ?

- HEALTH RISK IS HUGE IF UNTREATED
- IS TSH THE BEST CLINICAL MARKER ?
 - INSENSITIVE NEAR NORMAL
 - GETS TOO SMALL BEFORE FULL CLINICAL EFFECT
 - RECEPTOR ACTIVITY DOESN'T REFLECT METABOLIC DEMAND
- IS IODINE GOOD FOR THYROID FUNCTION ?
 - DECREASES THYROID FUNCTION IF NOT DEFICIENT
- ARE SYNTHETIC THYROID MEDS MORE PRECISE AND MORE SCIENTIFIC THAN NATURAL ?
 - NATURAL THYROID IS BIOIDENTICAL, U.S.P. AND HAS > EFFECT
 - HALF-LIFE IS LONG IN MOST THYROID MEDS
 - MOST PEOPLE END UP ON 2 SYNTHETIC MEDS
 - IF SYNTHROID ALONE CAN'T CONVERT T4 TO T3
 - IF CYTOMEL ALONE T4 GOES TO ZERO