to baseline was possible. The patient was treated with high dose decadron and successfully underwent a craniotomy. The treating physician felt this adverse event was probably related to Thyrogen administration and stated he will pretreat patients with intra-axial CNS lesions or skeletal lesions with steroids, to avoid local edema at the site of metastases.

4. A 71 yr. old F with calvarium and spinal cord metastases received Thyrogen 0.9 mg IM on 2 consecutive days. On the day following the last dose, she was admitted to the hospital with neuropathy described as a "shocking sensation" radiating down both lower extremities resulting in leg numbness and weakness. The patient was treated with dexamethasone IV and external beam radiation therapy. She recovered without sequelae. The treating physician determined that this event was remotely/unlikely related to Thyrogen because she was experiencing similar symptoms prior to Thyrogen administration.

Evaluation and Regulatory Action:

The results from the 2 phase III controlled studies indicate that Thyrogen scanning and thyroglobulin are less sensitive than withdrawal to detect thyroid remnants and well-differentiated thyroid cancer.

In the first phase III study, TSH92-0601, the scan discordant rate significantly favored WD over Thyrogen. Although in the second phase III study, TSH95-0101, the discordance rate was not statistically significant, the proportion of scans that were a higher classification significantly favored WD over Thyrogen. When the scans from the TSH92-0601 study were analyzed using the same scan rating criteria as used for TSH95-0101, the statistically significant difference in favor of the WD scan remained. There are several explanations for the scan outcome differences in these two studies:

1. A higher diagnostic activity of ^{131}I was administered in the TSH 95-0101 study: 4 mCi compared to 2-4 mCi in study TSH92-0601.

2. In study TSH95-0101, the scan were conducted for a minimum acquisition time and a minimum number of counts.

Whether statistically significant or not, both phase III studies demonstrated that scanning following THST withdrawal is more sensitive for detecting thyroid remnants and cancer. Using the 2 dose Thyrogen regimen, the Thyrogen scan failed to detect remnants/cancer localized to the thyroid bed in 9/65 (14%) patients with positive WD scans in study TSH92-0601 and in 6/45 (13%) patients with positive WD scans in study TSH95-0101. The corresponding incidence for missed metastatic disease with Thyrogen scanning was 4/15 (27%) and 3/9 (33%), respectively. An important point is that there were only 15 patients in study TSH92-0601 who had WD scans that were positive for metastatic disease and, in study TSH95-0101, there were only 9 such patients. Therefore, the incidence of missed metastatic disease by Thyrogen scanning is significant. On the 3 dose regimen, Thyrogen scanning missed remnants/cancer in 6/56 (11%) patients with positive WD scans and missed metastatic disease in 2/14

(14%) patients with positive scans in study TSH95-0101. There were only 14 WD scans that were positive for metastatic disease in arm II (3 dose regimen) in study TSH95-0101.

There are two possible reasons physiologically why WD scanning is more sensitive than Thyrogen scanning:

1. ^{131}I uptake is related to the rise in TSH as well as to the duration of time TSH is elevated (Schlumberger et al JCEM 57(1):148-151, 1983) and

2. ^{131}I kinetics differs between the hypothyroid and the euthyroid states.

The longer the duration of time TSH is elevated, the higher the uptake. TSH is elevated for several weeks following THST withdrawal compared to several days following Thyrogen administration. Furthermore, more ^{131}I is available for uptake into thyroid remnants and cancer during the hypothyroid state (WD) due to slower metabolism and decreased renal clearance of ^{131}I. This is reflected in the longer half-life, higher whole body retention and higher cumulative activity of ^{131}I in the hypothyroid state compared to the euthyroid state.

One should also bear in mind that in study TSH95-0101, the reading of the diagnostic scans using a side-by-side comparison only was potentially biased in favor of not seeing a difference even if one existed. This is clearly illustrated by the scan readings in study TSH92-0601 where 11 scan pairs were rated as concordant in a side-by-side comparison but were rated as discordant when read individually.

The diagnostic utility analyses demonstrate that Thyrogen Tg -/+ scan is not as sensitive as WD for detecting thyroid remnants and cancer. Despite doing both a scan and a Tg, Thyrogen misses 6-9% of cancers using the dosing regimen recommended by the sponsor (0.9 mg qd x 2 doses) in their draft label for the product. Missed cancers are even higher (12-19%) if the same cut-off is used to compare Thyrogen to WD, rather than using the downward adjusted cut-offs used by the sponsor. These false negative rates are high for a malignancy which is highly curable if detected early.

Furthermore, on this same 2 dose regimen, the combination of Thyrogen Tg and scan missed metastatic disease confirmed by the post-treatment scan in 2 patients at the 10 ng/ml cut-off which is significant given that there were only 9 patients treated with this dosing regimen who had scan confirmed metastatic disease. Patients die from undetected metastatic disease. Furthermore, per Schlumberger (J Nuc Med 33(1):172-173, 1992), the key to survival is to detect metastatic disease while the x-rays are still negative. Thyrogen Tg may be undetectable when the withdrawal Tg is >10 ng/ml, the cut-off used to alert the physician that metastatic disease may be present even if the diagnostic scan is negative.

Since a significant number of patients in the TSH95-0101 study had a Thyrogen Tg <10 mg/ml but the corresponding WD Tg was ≥10 ng/ml: 10/34 (29%) patients in arm I and 9/40 (23%) patients in arm II, the sponsor used receiver operator curves to determine how much of a downward adjustment in Thyrogen Tg was needed to try to maximally accommodate this difference between Thyrogen and

withdrawal (i.e. provide the best sensitivity and specificity possible given the Thyrogen Tg database in this study). Assigning 100% sensitivity and specificity to the WD Tg/scan and post-rx. scan reference standard as the sponsor did, a Thyrogen Tg of 10 ng/ml (obtained on the 2 dose regimen) is only 53% as sensitive as a withdrawal Tg of 10 ng/ml or a positive WD/post-rx. scan to detect thyroid remnants or cancer. It should be noted that the validity of the reference standard used by the sponsor is questionable because the reference standard included the WD scan and bias may have been introduced in the reading of the scans by doing only a side-by-side reading of the scan pair looking for concordance.

The Thyrogen diagnostic utility analyses conducted by the sponsor merely represent the best post-hoc fit of the Thyrogen Tg database in study TSH95-0101, and only in this study, to the study WD Tg and WD/post-rx. scan database. The bottom line is: at the Thyrogen dosing regimens studied, no correlation exists between Thyrogen Tg and WD Tg. This is readily apparent from examination of the FP (false positive) and FN (false negative) Thyrogen Tg levels relative to WD Tg. A given Thyrogen Tg level may be equivalent to, greater than or less than the corresponding WD Tg.

The clinical utility of thyroglobulin as a reliable surrogate marker for thyroid cancer in the follow-up of these patients, is predicated upon a consistent stimulation of thyroid tissue and proportionality to the tumor burden present. Consistent stimulation of thyroid tissue is critical to the clinical utility of any screening or diagnostic modality for this disease so that an increase in Tg from a previous level in a given patient is a reliable indicator of persistent or recurrent disease. Furthermore, to be useful as a diagnostic modality for this disease, it is critical that the Tg level be proportional to the tumor burden present. Because withdrawal Tg is proportional to the tumor burden present, it can be used to interpret the clinical significance of a negative or class 1 scan (note: the WD diagnostic scan has a FN rate as high as 10-35%). As Schlumberger states [J Nuc Med (33)1: 172-3, 1992): "The early discovery of metastases at a stage when x-rays are still normal, is the main prognostic factor for cure. In a given patient, the increase in Tg level is related to the size of the metastases..." At the doses studied, Thyrogen is an erratic stimulator of thyroid tissue. Therefore, not only can we not interpret the clinical significance of a given Thyrogen Tg level but we cannot use it as a reliable surrogate marker for cancer in the long-term follow-up of these patients. Hence, it has no clinical utility either as a screening test or as a diagnostic agent at the doses studied.

One can postulate that the erratic thyroglobulin levels on Thyrogen relative to withdrawal, is related to an insufficient period of TSH stimulation of thyroid tissue (not priming the thyroid tissue for a sufficient period of time to adequately stimulate Tg production). It has been demonstrated that the elevation in Tg is a function of both the rise in TSH as well as the duration of time TSH is elevated. The mean/median Tg levels on WD are higher than those on Thyrogen due to the prolonged

period of TSH stimulation following THST WD compared to only an acute rise in TSH on Thyrogen. It is possible that with a more prolonged period of administration, Thyrogen would be a consistent stimulator of thyroid tissue and would be equivalent to withdrawal. To be approved as an alternative to withdrawal, Thyrogen must be equivalent to withdrawal. Following the sponsor's presentation of the data from study TSH92-0601 and **prior to the conduct of TSH95-0101**, the **Agency sent a letter to the sponsor on June 23, 1995, in which we stated the following:**

"Perform another dose-ranging study with more patients per dosing regimen in order to determine a more effective dose and duration for administration of Thyrogen."

"Evaluate daily vs. alternate-day administration of Thyrogen because of the unexpectedly long half-life of Thyrogen and the possibility that a longer period of stimulation will prove more effective."

In the follow-up of patients with thyroid cancer, Schlumberger recommends (NEJM 338:5:297-306, 1998) only yearly follow-up and no need for a total body scan if the WD Tg is <1 ng/ml. Conversely, he recommends administration of a therapeutic dose of radioiodine if the WD Tg is >10 ng/ml. If we apply Schlumberger's algorithm to Thyrogen, we would be scanning and treating every patient who receives Thyrogen. This is because a Thyrogen Tg $\leq$0.5 ng/ml may be >10 ng/ml if the patient were withdrawn. The sponsor recommends that a Thyrogen Tg and a scan be performed in every patient when it is to be used as an alternative to withdrawal. Unnecessary scanning, is not without risk. Stunning may occur. Furthermore, a higher diagnostic activity of ^{131}I is necessary for Thyrogen scanning (4 mCi was used in the second phase III study) than for withdrawal scanning to compensate for the more rapid clearance of radioiodine in the euthyroid state compared to the hypothyroid state. This may also contribute to stunning (whereby the tissues concentrating ^{131}I have received a sufficient diagnostic activity of radioiodine that will diminish subsequent uptake of a therapeutic dose and, thereby, prevent cell killing. This is of particular concern with a metastatic focus. This is why the American Association of Clinical Endocrinologists recommends limiting scanning doses to 2-3 mCi- 1997 AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma by S. Feld). Furthermore, not only is a higher dose of ^{131}I required for diagnostic Thyrogen scanning, but a higher dose of ^{131}I is likely to be necessary for therapeutic purposes to obtain uptake of ^{131}I into the tumor which is comparable to the hypothyroid state. Unnecessary radioiodine treatment and/or delivery of a higher therapeutic dose includes an increased risk of bone marrow suppression and leukemia.

In addition to the safety concerns raised by missing cancer, overscanning and overtreatment, there is the concern of precipitating acute changes in tumor size which may be related to acute edema and/or hemorrhage as manifest by 3 patients with cerebral or spinal cord metastases who were treated with Thyrogen on a compassionate basis. The possibility that an acute increase in TSH induced by Thyrogen precipitated these adverse events

cannot be ruled out. One of the treating physicians stated he would, in the future, pretreat patients with cerebral or spinal cord metastases with steroids before administering Thyrogen.

In summary, the potential risks of Thyrogen administration, missed cancers, overscanning, overtreatment and the potential adverse events associated with an acute rise in TSH, outweigh the benefits of avoiding hypothyroidism, which may be for 2 weeks if the patient is switched from T4 to T3 therapy prior to withdrawal. Moreover, because Thyrogen, at the doses studied, is an inconsistent stimulator of thyroid tissue, the Tg levels on Thyrogen bear no correlation to withdrawal Tg nor are they proportional to the tumor burden present.

Regulatory Action:

Not Approvable

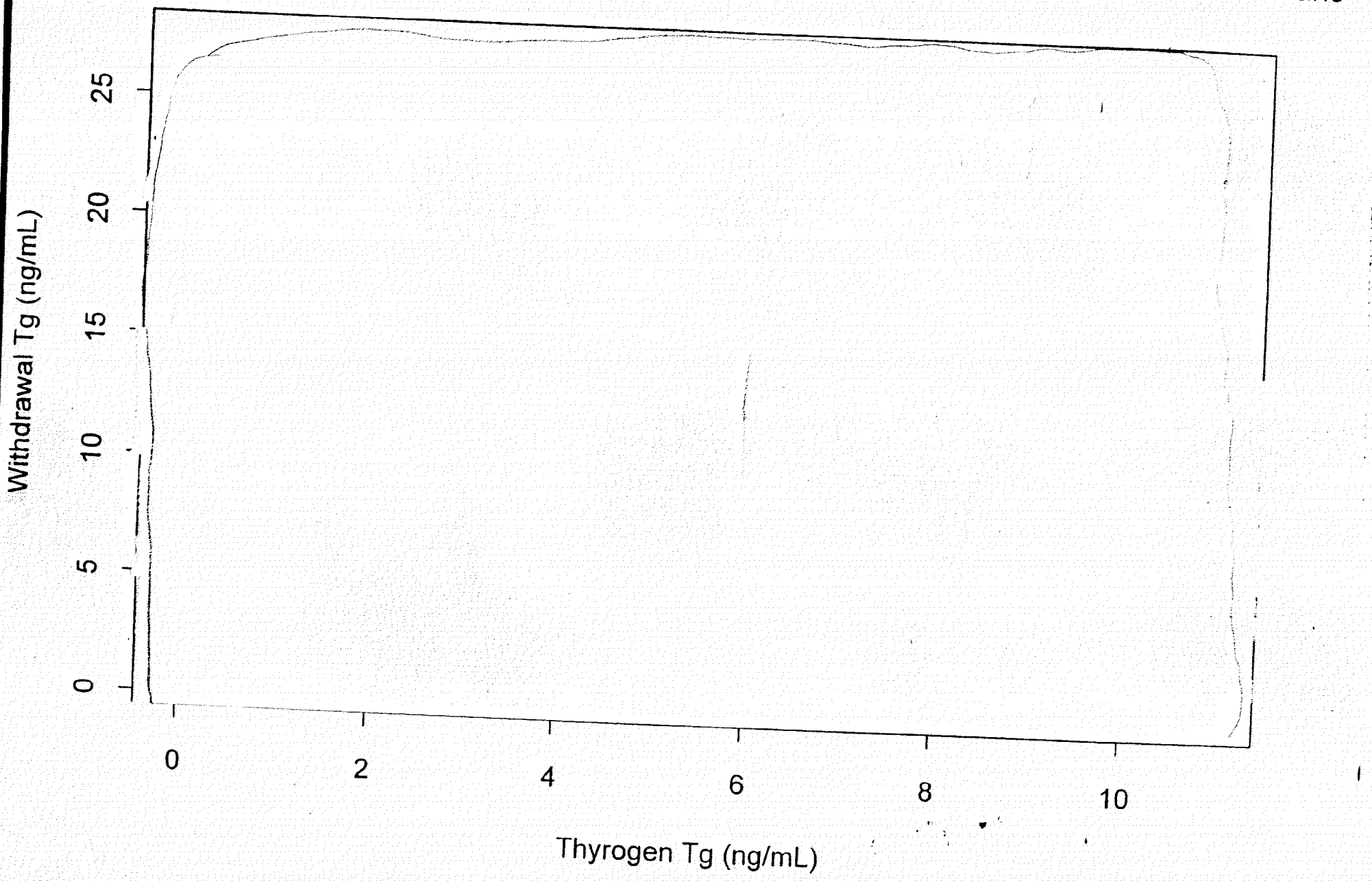
/S/ 4/9/98

Jean Temeck, M.D.

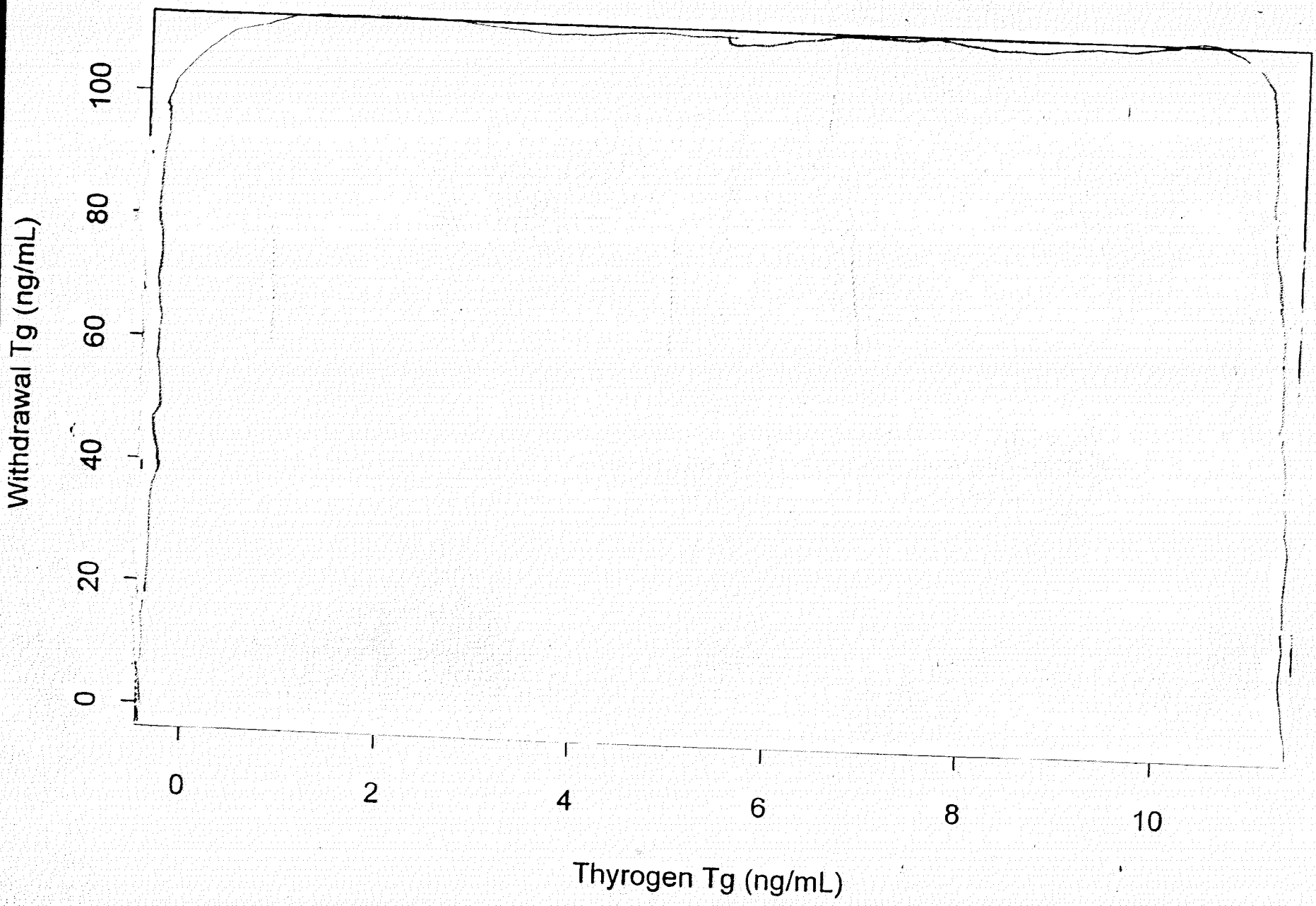
cc. NDA. Arch.20898
HFD-510 Div file
HFD-510/ Dr. Sobel/Dr. Orloff/Dr. Ahn/Dr. Fossler/Mr. McCort
HFD-720/Dr. Castillo

/S/ 4-20-98

Subjects in Arm I with Thyrogen Tg Values <10 ng/mL and Class 0 or 1 Withdrawal Scans



Subjects in Arm 2 with Thyrogen Tg Values <10 ng/mL and Class 0 or 1 Withdrawal Scans



Subjects in Arm 2 with Thyrogen Tg Values <10 ng/mL and Class 0 or 1 Withdrawal Scans

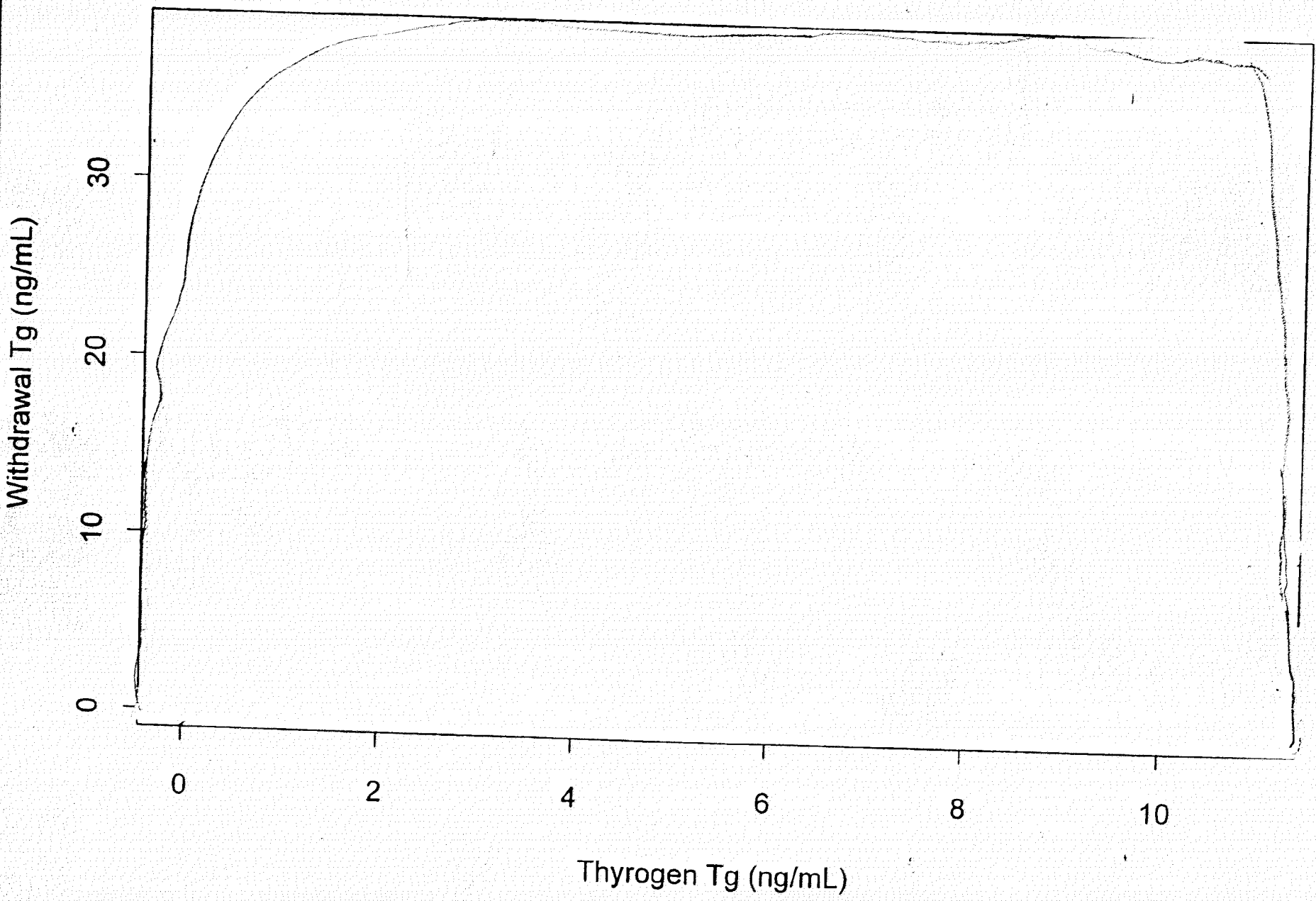


Figure 6.1.0

MEAN OF PATIENT SERUM TSH LEVEL
AFTER THYROGEN ADMINSTRATION
ARM I

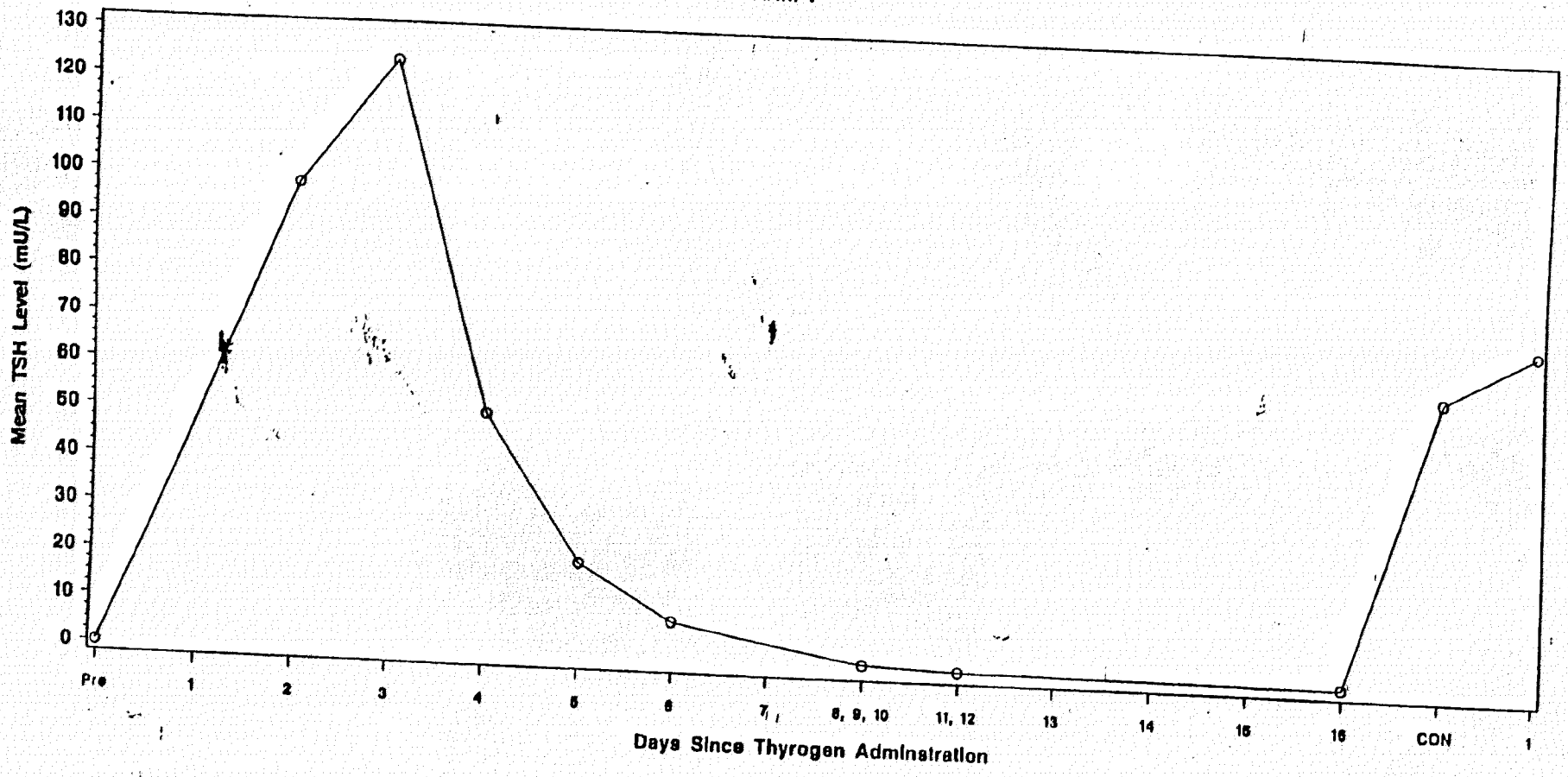


Figure 8.1.1

MEAN OF PATIENT SERUM TSH LEVEL
AFTER THYROGEN ADMINSTRATION
ARM II

APPEARS THIS WAY
ON ORIGINAL

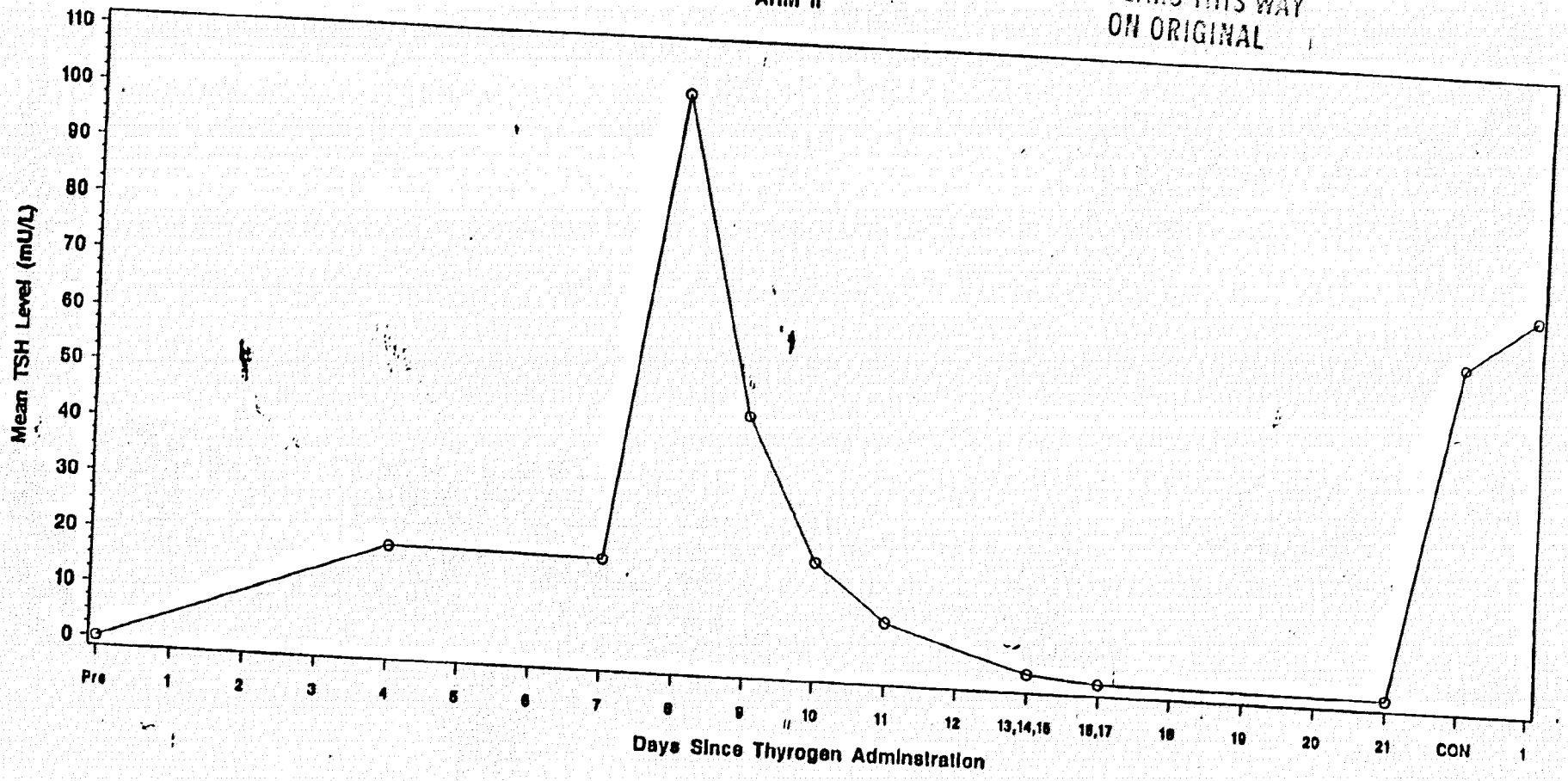
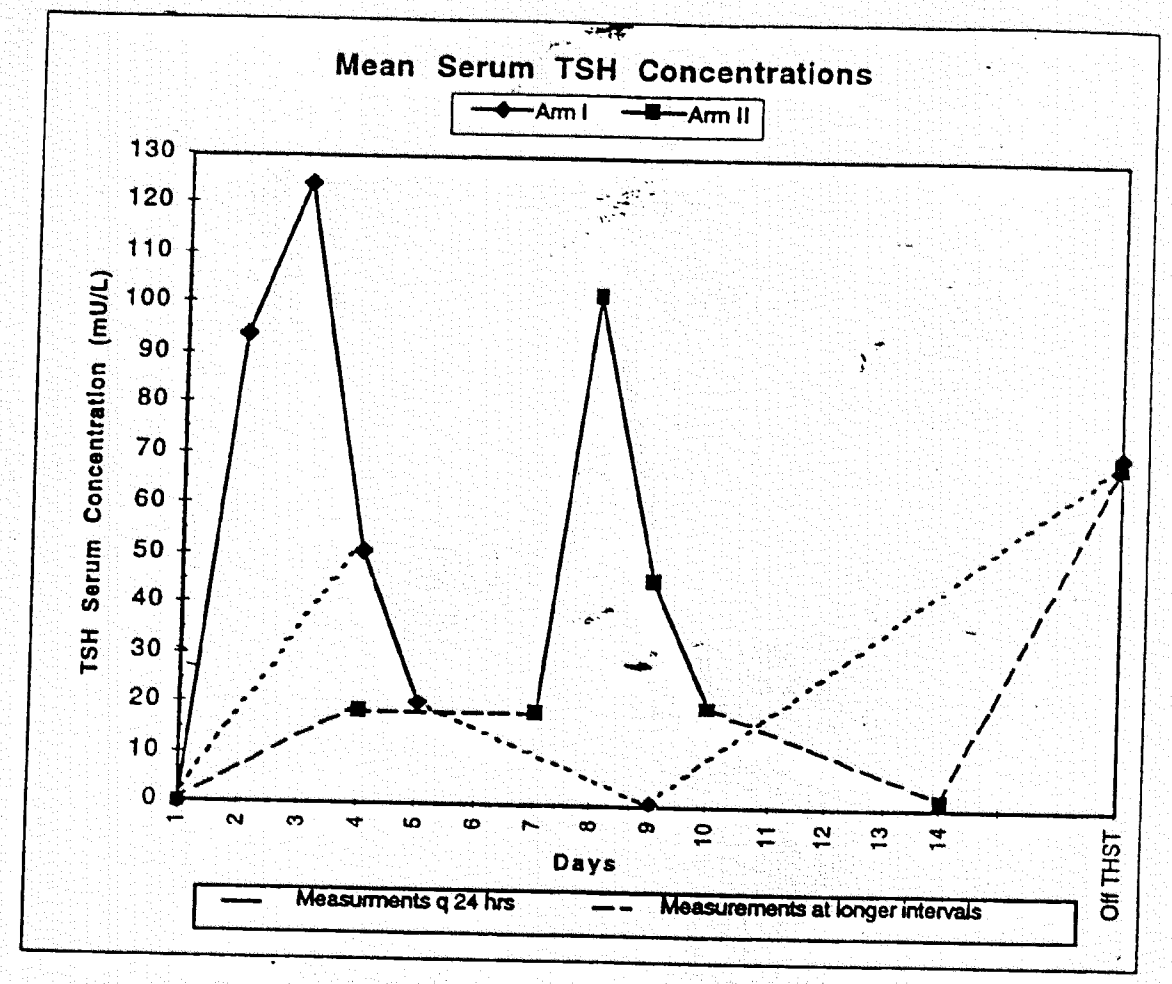


Figure 8.1.2



mccort

SEP 22 1997

IND: [redacted]
Drug: Thyrogen
Sponsor: Genzyme

Date submitted: 7/11/97
Date received: 7/14/97
Date reviewed: 8/27/97

Title of protocol: A MultiCenter, Open-Label, Randomized, Cross-Over Dosimetry Study of Radioiodine (^{131}I) Uptake During Euthyroid States Following the Administration of Thyrogen (thyrotropin alfa) and Hypothyroid States During Thyroid Hormone Withdrawal (Protocol TSH97-0401)

Objectives:

This study evaluates the hypothesis that quantitatively lower ^{131}I thyroid uptake and whole body retention characteristics observed after Thyrogen administration may be explained by differences in clearance of ^{131}I from the body during the euthyroid and hypothyroid states. During the hypothyroid state, ^{131}I levels remain elevated because ^{131}I clearance is decreased. In order to deliver an ablative radiation dose to thyroid remnants when patients are euthyroid with the use of Thyrogen, higher administered activities of ^{131}I may be required.

The primary objective of this study is to compare the calculated administered activity of ^{131}I required to deliver 30,000 rad (cGy) to thyroid remnant during euthyroid states after Thyrogen administration and during hypothyroid states after thyroid hormone suppressive therapy (THST) withdrawal. The calculation of administered ^{131}I will be based on differences observed in ^{131}I kinetics during euthyroid states after Thyrogen administration and during hypothyroid states after THST withdrawal.

The secondary objective is to examine the hypothesis that the lower percent of radioiodine uptake in thyroid remnant during the euthyroid state following Thyrogen administration correlates with the more rapid clearance of radioiodine from the blood during the euthyroid state as compared to the hypothyroid state. Specifically, the previous finding that there is an ~50% decreased uptake of ^{131}I into the thyroid remnant and ~50% increase in clearance of ^{131}I in pts. who are euthyroid on Thyrogen will be confirmed.

Background, rationale and proposed methodology:

The 2-way x-over design was selected for the intra-patient comparison of dosimetric assessments for several reasons. First, there is a range of opinion regarding the optimal surgical procedure(s) for thyroidectomy in pts. diagnosed with well-differentiated thyroid cancer. Each procedure results in varying amounts of residual thyroid tissue. The 2-way x-over design controls for the potential effect of inter-patient variability regarding the extent of residual thyroid tissue present following total or near-total thyroidectomy.

Second, estimating remnant tissue mass is critical for

conducting accurate quantitative radiation dosimetry assessments, but the process of quantifying mass is complex and often difficult. The complexity of the process introduces a component of error into the dosimetric calculations. The random x-over design uses the patient as his own control and, consequently, the mass of residual thyroid tissue will be consistent for the diagnostic dosimetry study. Sequential images will be acquired to generate activity-time curves for remnant tissue, whole body and blood.

Finally, the x-over design controls for any effect on study outcomes that could be the result of the sequence of Thyrogen and hormone withdrawal (wd) TSH stimulation. The x-over design used in this study allows for a direct quantitative comparison of remnant uptake and retention characteristics, and whole body retention when a pt. is euthyroid after Thyrogen and hypothyroid during thyroid hormone wd.

During this study, standardized, quantitative, patient-specific dosimetry methodology will be used to determine the ratio of administered activity (mCi/MBq) of ^{131}I required to deliver an ablative radiation dose of 30,000 rad (cGy) to thyroid remnant and cancerous tissue when pts. are euthyroid on Thyrogen and hypothyroid after hormone wd. This quantitative approach is preferable to an empiric approach which administers a fixed ^{131}I treatment activity to all pts., because the former approach has been shown to have a higher success rate. Quantitative data acquisition procedures will be employed to determine remnant uptake; and whole body, blood and remnant retention characteristics following the delivery of a diagnostic administered activity of ^{131}I when pts. are euthyroid and hypothyroid. This quantitative approach entails sequential imaging of the patient at prescribed time intervals optimally using the conjugate view (180° opposed) technique with a dual-head [redacted]. These sequential images will be used to generate activity-time curves for remnant tissue, whole body and blood. From the integration of the activity-time curves, the cumulated activity (area under the curve) will be used to provide the residence time which normalizes the cumulated activity by the administered activity. In accordance with the established schema (which provide a relationship between radiation emitted from a source and energy absorbed in the target) of the Medical Internal Radiation Dose (MIRD) Committee of the United States Society of Nuclear Medicine, the residence time and relevant physical parameters will be used to calculate the radiation dose delivered to remnant tissue per unit administered activity (rad/mCi, cGy/MBq) when pts. are euthyroid on Thyrogen and hypothyroid after hormone wd.

Data collected during the dosimetry phase will be forwarded to the Dosimetry Coordinating Center (DCC) located at the

Division of Nuclear Medicine at the University of Cincinnati Medical Center. The DCC will be responsible for determining the ratio of administered activity (mCi/MBq) of ^{131}I required to deliver an ablative radiation dose when pts. are euthyroid on Thyrogen and hypothyroid after hormone wd. Information regarding ^{131}I uptake (comparison between the absolute activity and the administered activity, activity-time curve), cumulated activity and residence time in the thyroid bed will be collected to determine this ratio. This ratio will be used by the investigational sites to determine the amount of administered activity required to deliver a radiation dose of 30,000 rad (cGy). However, as physicians may determine that a different dose is more appropriate, the administered activity delivered will remain at the discretion of the investigator. A committee of investigators and a Genzyme representative will be convened to discuss each of these deviation cases.

Since higher administered activities of ^{131}I may be used for ablation with Thyrogen, whole body and blood ^{131}I measurements will be taken to provide information on retention and clearance characteristics. Although higher administered activities of ^{131}I may be used, it is not anticipated that this will result in higher radiation doses to the whole body because of the more rapid clearance of ^{131}I from the body during the euthyroid state.

Post-ablation ^{131}I imaging will be conducted 7 to 14 days following ablation to document the uptake of ^{131}I within the targeted thyroid remnant tissue. The ^{131}I percent uptake within the thyroid remnant will be measured at the time of ^{131}I imaging.

Note: The Dosimetry Coordinating Center (DCC) will be responsible for training all study site personnel to ensure the uniform quality of data obtained from the WBS scanning procedures and remnant conjugate image pairs (obtained on Thyrogen and during wd of THST). These images will be obtained using a dual-head, gamma camera scanning system equipped with high energy collimators (for ^{131}I), triple window simultaneous image acquisition capability, and quality control and calibration materials/sources. A data acquisition computer will be required for collecting scintillation camera digital data.

Patient iodine biokinetics will be assessed to evaluate whole body and blood retention (%), activity-time curves, clearance (hrs.) and cumulated activity. See enclosed schema regarding days on which urine and blood will be collected for these determinations. The activity-time curves generated for the blood will be used with the whole body (minus blood) retention data to calculate dose to the blood according to the method of Benua and through newer MIRD-based methods involving vessel specific parameters.

Protocol: