The study is a multi-center, open-label, randomized, 2-way x-over study. 40 pts. (to achieve a total of 11 evaluable pts. enrolled in each of two study sequences) ≥ 18 yrs. who recently have undergone a total or near-total surgical thyroidectomy for well-differentiated (papillary, follicular or Hurthle cell) thyroid cancer and who are scheduled to undergo ^{131}I diagnostic imaging prior to initial ablation will be enrolled. This pt. population was selected because typically these pts. have remnant tissue that is able to concentrate sufficient ^{131}I in the thyroid bed to conduct quantitative radiation dosimetric evaluations. Remnant tissue is predominately normal thyroid tissue that has a higher iodine avidity than malignant tissue. Studying pts. prior to initial rx. will avoid any impact of previously administered rx. activities of ^{131}I on tissue iodine avidity. The presence of remnant tissue must be confirmed by imaging (e.g. ^{99m}Tc scan or ultrasound).

After initial thyroid surgery, pts. must wait a minimum of 6 wks. before they are eligible for study enrollment to minimize the lingering effects of surgery (e.g. edema) and allow stabilization of endogenous thyroid hormone levels. During these 6 wks., pts. will be maintained on THST to achieve serum TSH levels ≤0.5 mU/L for at least 4 wks., but not longer than 12 wks. after thyroidectomy. To minimize the potential for iodine burden interference with study measurements, pts. should not receive any iodine-containing contrast agents prior to enrollment. To facilitate ^{131}I uptake, all study pts. will follow a low-iodine diet and avoid the use of meds (including vitamins) containing iodine, iodine-containing antiseptic soaps and surgical scrubs for 2 wks. before whole body imaging procedures.

All pts. must be designated as within the low risk cancer classification (pts. < 45 yrs. with TNM Stage I cancer: T, MO and N1a only or pts. ≥ 45 yrs. with TNM Stage I or TNM Stage II cancer).

Female pts. must have a negative pregnancy test within 5 days of ^{131}I administration and must be following an approved mode of contraception.

Among the exclusion criteria are: anaplastic or medullary thyroid cancer, lymphoma of the thyroid gland, pituitary dysfunction; high risk cancer classification, non-thyroidal conditions effecting iodine uptake (e.g. CHF or renal failure), any IV water soluble radiographic contrast administration within the previous 4 wks., intrathecal or cholecystographic iodinated contrast agent administration within the previous 3 mos., on concurrent meds affecting thyroid or renal function (e.g. renal drugs, lithium or corticosteroids); and pregnant or nursing women.

The following screening evaluations will be performed:

a complete hx. and physical exam; CBC; serum chemistry;

blood for Tg, Tg antibody and antibodies to Thyrogen; UA; pregnancy test; and ^{99m}Tc pertechnetate scan and/or ultrasound to determine thyroid remnant mass.

Following screening, pts. will enter the Dosimetry Phase of the study. Two quantitative radiation dosimetry assessments will be conducted on each study patient. Each patient will be randomized to one of two sequences:

Dosimetry Phase: Sequence A:

Hypothyroid state:

Pts. randomized to Sequence A begin the dosimetry phase in the hypothyroid state resulting from thyroid hormone wd. Wd will be of adequate duration to allow serum TSH levels to increase $\geq$ 25 mU/L prior to administration of ^{131}I. A 2 mCi (74 MBq) (±10%) diagnostic administered activity of ^{131}I will be given orally at least 3 hrs. after the patient's last meal and 2 hrs. prior to the next meal, followed by a wd diagnostic WBI (whole body imaging) at 2, 6, 24, 48, 72 and 96 hrs. after ^{131}I administered activity.

Euthyroid state:

Suppressive doses of thyroid hormone will then be administered over a 4 wk. period to suppress TSH levels to $\leq$ 0.5 uU/ml. The pt. will then receive 2 IM injections of 0.9 mg of Thyrogen administered 24 hrs. apart. A 2mCi (74 MBq) (±10%) diagnostic administered activity of ^{131}I will be given orally at least 3 hrs. after the pt's last meal and 2 hrs. prior to the next meal, followed by a diagnostic WBI at 2, 6, 24, 48, 72 and 96 hrs. after ^{131}I administered activity.

Dosimetry Phase: Sequence B:

Euthyroid state:

Pts. randomized to Sequence B begin the dosimetry phase while in the euthyroid state after administration of suppressive doses of thyroid hormones (to suppress TSH levels to $\leq$0.5 uU/ml). All pts. will receive 2 IM injections of 0.9 mg Thyrogen administered 24 hrs. apart. After Thyrogen administration, a 2 mCi (74 MBq) (±10%) diagnostic administered activity of ^{131}I will be given orally at least 3 hrs. after the pt's last meal and 2 hrs. prior to the next meal, followed by a diagnostic WBI at 2, 6, 24, 48, 72 and 96 hrs. after ^{131}I administered activity.

Hypothyroid state:

Pts. will then be wd from THST to make them hypothyroid and with a serum TSH $\geq$ 25 mU/L prior to the administration of ^{131}I. A 2 mCi (74 MBq) (±10%) diagnostic administered activity of ^{131}I will be given orally at least 3 hrs. after the pt's last meal and 2 hrs. prior to the next meal, followed by a wd diagnostic WBI at 2, 6, 24, 48, 72 and 96 hrs. after ^{131}I administered activity.

Ablation Phase:

Within 5 days of the second series of diagnostic assessments, pts. within each sequence will receive ^{131}I for ablation. Prior to ablation, pts. assigned to Sequence A will receive a second course of Thyrogen. Pts. in Sequence B will be in the hypothyroid state and will proceed directly to ^{131}I ablation procedures. Administration of ^{131}I for ablation will occur 24 hrs. after the final injection of Thyrogen. The Dosimetry Coordinating Center (DCC) will be responsible for forwarding information regarding the amount of ^{131}I (ratio of administered activity: mCi/MBq) required to deliver an ablative, targeted radiation dose of 30,000 rad (cGy) to remnant thyroid tissue.

After ablation, 3 whole body probe evaluations will be conducted on 3 separate occasions, 8-12 hrs. apart to obtain whole body ^{131}I activity measurements. These measurements must be obtained within 3 days following ablation. Post-ablation ^{131}I imaging will be conducted 7 and 14 days ($\pm$3 days) later, at least 48 hrs. apart, to document the distribution of uptake within the thyroid bed and whole body.

Tests and Evaluations:

Time 0 will be defined as the point when procedures begin. Specific parameters of interest include ^{131}I thyroid remnant uptake, retention characteristics, cumulated activity and ^{131}I biokinetics.

Procedural Flow Diagrams and Flow Charts are enclosed.

Note: After randomization, if a patient is diagnosed with metastatic cancer requiring timely therapy during the first sequence, the physician may proceed directly to ^{131}I therapy. These patients will be replaced to meet sample size requirements.

Statistical Considerations:

The sample size of 22 evaluable pts. (11 pts. in each sequence) will allow > 80% power to detect a difference in means of ^{131}I whole body retention of 5% between Thyrogen euthyroid states and hypothyroid states, assuming a standard deviation of 7.850, with a two-tailed test at the 0.05 significance level. The sample size calculation was determined by using the whole body retention data since this represents the most reliable iodine biokinetics data collected to date.

Study Endpoints:

The primary endpoint of this study is to identify 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 when pts. are euthyroid on Thyrogen and hypothyroid after

hormone wd. To determine this ratio, the following variables will be evaluated during euthyroid and hypothyroid states: ^{131}I uptake in the thyroid bed, activity-time curves, cumulated activity and residence time.

Secondary endpoints are to identify and compare ^{131}I clearance and cumulated activity in the whole body and blood during euthyroid and hypothyroid states. To determine this difference, the following variables will be determined during euthyroid and hypothyroid states: ^{131}I activity-time curves, clearance (hrs.) and cumulated activity in the whole body and blood. In addition, differences in creatinine clearance rates will be evaluated during euthyroid and hypothyroid states.

The statistical analysis of these endpoints will be performed in the framework of the following model:

Response= Overall Mean + Sequence + Subject (Sequence) +
Treatment by Sequence (Period) + Treatment + Error

The sequence effect will be tested using the subject (sequence) as an error term. All other effects will be tested using the error term.

If there is no sequence effect, the effects of the treatments will be compared using the T-test with model error term. If there is a period effect or sequence effect, then the treatment effects will be compared using the first period only.

Evaluation and Regulatory Action:

The study is based on sound scientific rationale and is well-designed to answer its stated objectives. Informed consent will be obtained. Scan imaging procedures include quality control and quality assurance measures. The study is, therefore, approved.

The following suggestions should be conveyed to the firm:

3. In the unlikely event that an area(s) of uptake are visualized only on the post-treatment scan, describe how the patient(s) will be handled. individual therapeutic

4. Specify your criteria for success.

6. Measure thyroglobulin antibody on the same days as serum thyroglobulin.

7. Will treatment in patients with positive cervical lymph nodes include surgical dissection prior to ^{131}I therapy?

8. Be specific in terms of your plans to monitor patients

for the potential acute and long-term adverse effects of ^{131}I therapy.

9. Please submit a list of study sites and investigator curriculum vitaes.

9/12/97: Discussed ≈ Dr. Orloff - Convey key points 3, 4, 6, 7, 8 + 9 to sponsor

/S/

Jean Temeck, M.D. 9/2/97

cc. IND [redacted].Arch
HFD-510/Dr. Orloff and Mr. McCort
HFD-510 Division file

/S/
9/22/97.

/S/
9-22-97

APPEARS THIS WAY
ON ORIGINAL

thyroid remnant and non-thyroidal tissue per administered activity (mCi/MBq) is provided in Appendix I.

3.5.1 Procedural Flow Diagrams

The following procedural diagrams provide comprehensive information regarding the study procedures and evaluations to be performed during the conduct of the study.

Diagram 2A

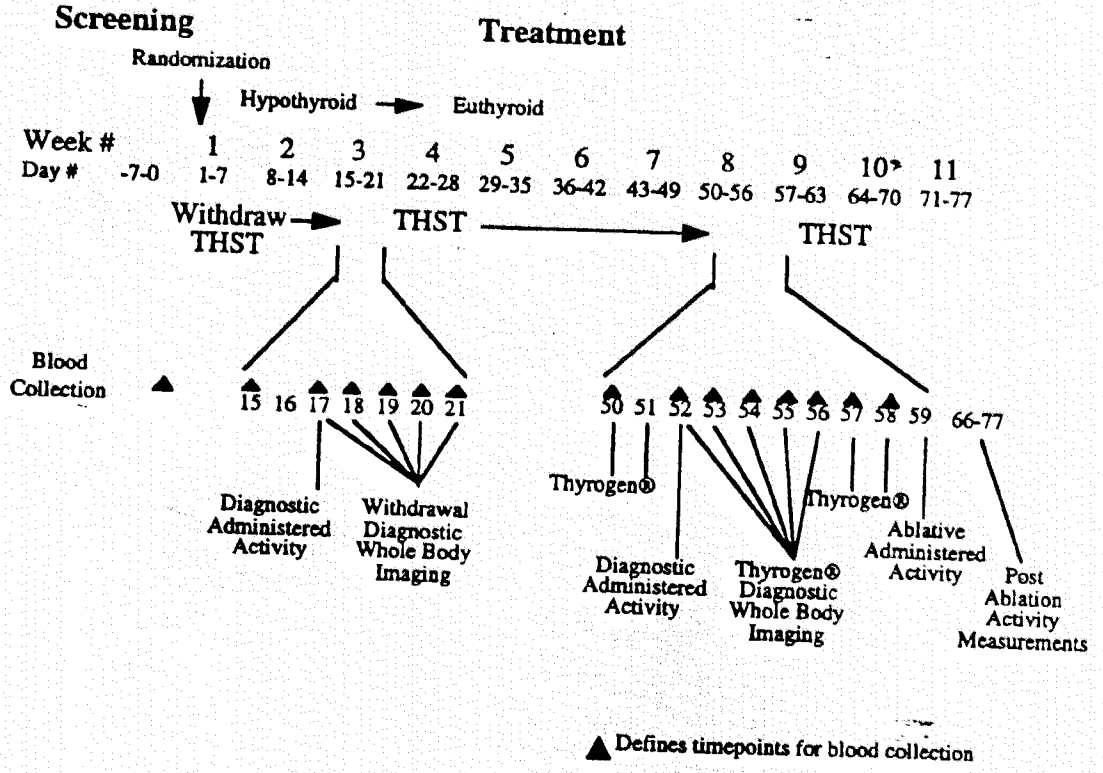

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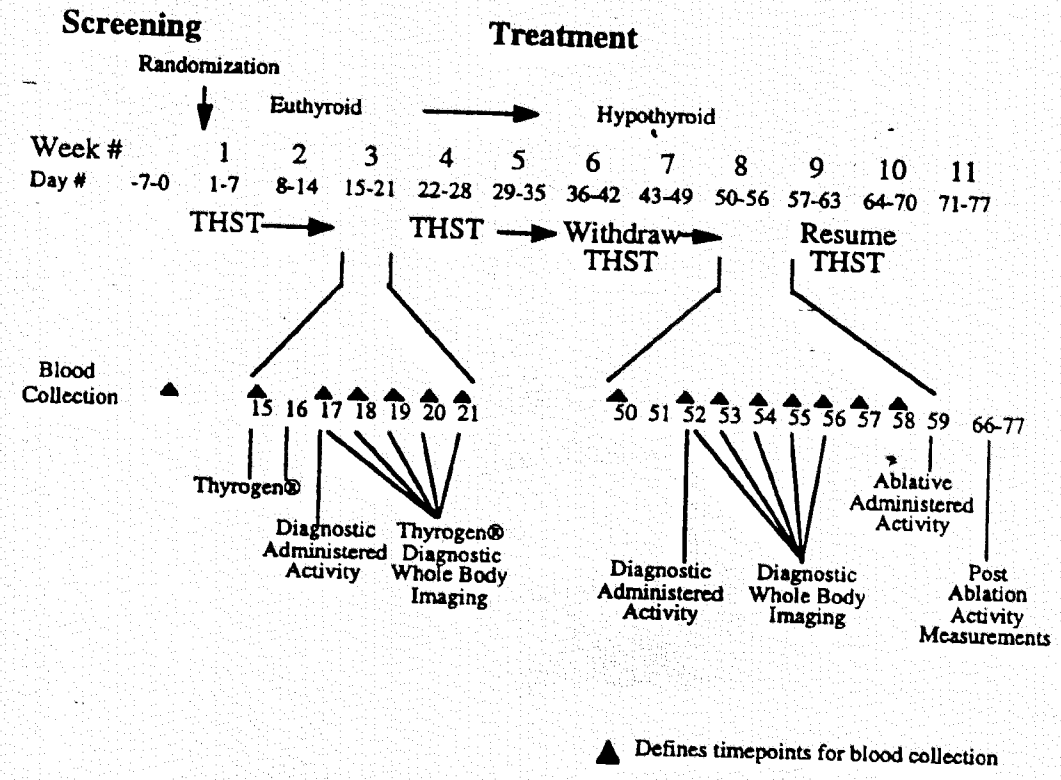
Diagram 2B



▲ Defines timepoints for blood collection

3.5.2 Study Provisions

APPEARS THIS WAY
ON ORIGINAL

3.5.2.1 Dosimetry Operations Manual

Prior to study initiation, all sites will be required to review the Dosimetry Operations Manual (DOM). The DOM will establish guidelines for conducting the procedures described in the study protocol. Some examples of these procedures include:

- Determination of thyroid remnant mass
- Whole body and thyroid bed ^{131}I-imaging and analysis
- Data acquisition procedures from whole body and thyroid bed ^{131}I images

Flowchart 1A

SEQUENCE A

Tests and Evaluations	Screening	Week 0 Day -7-0	Week 1-2 Day 1-14	Week 3 Day 15	Week 3 Day 16	Week 3 Day 17	Week 3 Day 18	Week 3 Day 19	Week 3 Day 20	Week 3 Day 21	Week 4-5 Day 22-35	Week 6-7 Day 36-49	Week 8 Day 50	Week 8 Day 51	Week 8 Day 52	Week 8 Day 53	Week 8 Day 54	Week 8 Day 55	Week 8 Day 56	Week 9 Day 57	Week 9 Day 58	Week 9 Day 59	Week 9 Day 60-63	Week 10 Day 64-67	Week 11 Day 71 77
		Diag Admin. Activity 2 hrs. 6 hrs. 24 hrs. → 48 hrs. → 72 hrs. → 96 hrs. →																							
		Treatment																							
Informed Consent	X																								
Medical History	X																								
Physical exam	X																								
Vital signs	X					X																			X
Diagnostic Administered Activity						X[2]									X										X
Ablative Administered Activity															X[2]										
Hematology	X		X																		X5				
Blood chemistry	X		X										X												X
Urinalysis	X												X												X
Pregnancy test (If applicable)	X		X																						X
Antibody to Thyrogen®	X												X												
Thyroglobulin	X		X		X	X	X	X	X				X												X
TSH	X		X		X	X	X	X	X				X		X	X	X	X	X						X
THYROGEN® Dosing													X		X	X	X	X	X						X
24 Hour Creatinine Clearance			X3										X	X						X	X				
Blood for Iodine Kinetics						X	X	X	X	X			X3												
Urine for Iodine Kinetics	X		X												X	X	X	X	X			X	X	X	X
Whole Body Imaging						X	X	X	X	X			X												
Whole Body Probe															X	X	X	X	X5				X2	X3	
THST	X																					X4			
Adverse Events / Concomitant Medications											X														
		Monitor / record throughout the study as described in section 3.7.1																							

1. Serious adverse events only up to 3 months post-ablation
2. Imaging on Day 7 and Day 14 are to be performed +/- 3 days, at least 48 hours apart, whenever possible.
3. Urine collection for 24 hour creatinine clearance to be initiated at indicated and continued for 24 hours.
4. Whole Body Probe to be performed up to 3 times, 8-12 hours apart, within 3 days after ablation.
5. The ablative administered activity must be given within 5 days of the completion of the second dosimetric assessment.

Flowchart 1B

SEQUENCE B

Week 0	Week 1-2	Wk 3							Week 4-5	Week 6-7	Week 8						Week 9				Week 10	Week 11
Day -7-0	Day 1-14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22-35	Day 36-49	Day 50	Day 51	Day 52	Day 53	Day 54	Day 55	Day 56	Day 57	Day 58	Day 59	Day 60-63	Day 64-67	Day 71 77
				Diag Admin. • Activity 2 hrs. 6 hrs. 24 hrs. → 48 hrs. → 72 hrs. → 96 hrs. →								Diag Admin. • Activity 2 hrs. 6 hrs. 24 hrs. → 48 hrs. → 72 hrs. → 96 hrs. →											

Tests and Evaluations	Screening	Treatment																					
Informed Consent	X																						
Medical History	X																						
Physical exam	X																						
Vital signs	X				X								X										X
Diagnostic Administered Activity					X*								X*										X
Ablative Administered Activity																							
Hematology	X		X								X									X5			
Blood chemistry	X		X								X												X
Urinalysis	X																						X
Pregnancy test (if applicable)	X		X								X												X
Antibody to Thyrogen®	X										X												
Thyroglobulin	X		X		X	X	X	X	X		X		X	X	X	X	X						X
TSH	X		X		X	X	X	X	X		X		X	X	X	X	X						X
THYROGEN® Dosing			X	X																			X
24 Hour Creatinine Clearance			X3								X3												
Blood for Iodine Kinetics					X	X	X	X	X				X	X	X	X	X						
Urine for Iodine Kinetics	X		X								X									X	X	X	
Whole Body Imaging					X	X	X	X	X				X	X	X	X	X5				X2	X2	
Whole Body Probe																				X4			
THST	X →																					X →	
Adverse Events / Concomitant Medications	Monitor / record throughout the study as described in section 3.71																				X	X	

1. Serious adverse events only up to 3 months post-ablation
2. Imaging on Day 7 and Day 14 are to be performed +/- 3 days, at least 48 hours apart, whenever possible.
3. Urine collection for 24 hour creatinine clearance to be initiated as indicated and continued for 24 hours.
4. Whole Body Probe to be performed up to 3 times, 8-12 hours apart, within 3 days after ablation.
5. The ablative administered activity must be given within 5 days of the completion of the second dosimetric assessment.

NDA: 20,898
Drug: Thyrogen
Sponsor: Genzyme

Date submitted: 5/13/98
Date received: 5/15/98
Date reviewed: 5/20/98

Thyrogen Safety Update:

This update addresses the safety data collected in the Compassionate Use Program from July 1, 1997 through March 31, 1998. An additional 70 patients were enrolled during this period. 7 patients experienced serious adverse events, 5 of these 7 died. None of the deaths were attributed to Thyrogen by the treating physicians. No case histories are provided in any of these deaths. Cardiac/respiratory failure/arrest were listed as adverse events in 4 of the 5 patients who died. In the remaining death, the following were listed as serious adverse events: progressive cancer, pleural effusion, deep vein thrombosis and pneumonia.

The serious adverse events in the 2 remaining patients who recovered were:

-pain at the site of a rib metastasis with onset 2-3 days after the second injection of Thyrogen. The patient recovered after surgical removal of the tumor.

- focal cerebral hemorrhage at the site of brain metastasis and acute pain and enlargement at site of rib lesion. These adverse events occurred 24 hrs. after the second Thyrogen injection. MRI of brain revealed a single frontal lesion with adjacent edema. A baseline MRI of the brain before Thyrogen administration had not been performed, so a comparison of the lesion size before and after Thyrogen administration was not possible. The patient received high dose Decadron and underwent a craniotomy. The pathology examination revealed focal hemorrhage. It was the investigator's opinion, that the rib lesion enlargement was due to edema at the site of metastasis. These events were deemed to be probably related to Thyrogen.

Evaluation and Regulatory Action:

There are now 4 patients with CNS metastases who experienced focal edema/hemorrhage at the site of the metastasis. These 4 cases will be included in the Adverse Reactions section of the label. Treatment with corticosteroids prior to Thyrogen administration may be helpful under such circumstances to reduce edema.

The following should be requested of the sponsor:

Submit case report forms for the 5 patients who died and were reported in the safety update.

/S/
Jean Temeck, M.D.
/S/
5-27-98

cc: NDA. Arch. 20898
HFD-510: Dr. Orloff/Mr. McCort
HFD-510 Div. file

Scan results

The following table summarize the scan data from the phase 3 trials:

	# scan pairs by disease category	# (%) scan pairs in which Thyrogen scan missed disease detected by WD scan
TSH92 (0.9 mg IM qd x 2)		
positive for remnant or cancer in thyroid bed	50	9 (18)
metastatic disease	15	4 (27)
total positive	65	13 (20)
TSH95 (0.9 mg IM qd x 2)		
positive for remnant or cancer in thyroid bed	39	6 (15)
metastatic disease	9	3 (33)
total positive	48	9 (19)
TSH95 (0.9 mg q72 hrs x 3)		
TSH95 (0.9 mg IM q72 hrs x 3)		
positive for remnant or cancer in thyroid bed	44	6 (14)
metastatic disease	16	2 (12.5)
total positive	60	8 (13)

From the above, the Thyrogen scan failed to detect remnant and/or cancer localized to the thyroid bed in 16% (21/133) patients in whom it was detected by WD scan. In addition, the Thyrogen scan failed to detect metastatic disease in 23% (9/40) patients in whom it was detected by WD scan.

Thyroglobulin results

Thyrogen Tg was detectable ($\geq$ 0.5 ng/ml) in 100% (35/35) patients in whom metastatic disease was confirmed by a post-treatment scan or by lymph node biopsy. By contrast, Tg on THST was undetectable in 4 (11%) of these patients.

In this same cohort of 35 patients with confirmed metastatic disease, the Thyrogen Tg levels were below 10 ng/ml in 8 patients, ranging from 2.0-9.5 ng/ml (corresponding WD Tg levels were 11.8-108 ng/ml). All patients in this study with confirmed metastatic disease had Thyrogen Tg levels $\geq$ 2 ng/ml. The Thyrogen scan added little additional information, detecting metastatic disease in only one of these 8 patients.

When Thyrogen Tg testing is used as a diagnostic tool, bear in mind that Thyrogen Tg levels are generally significantly lower than those after withdrawal, are not predictive of what the corresponding level would have been after withdrawal, and should not be relied upon as a measure of extent of disease.

Based on the findings of the clinical trials, a newly detectable Tg level or an increase in Tg to a level ≥ 2 ng/ml after Thyrogen, even in the setting of a negative or low stage Thyrogen radioiodine scan, should prompt consideration of WD in order to more definitively establish location and extent of thyroid cancer.

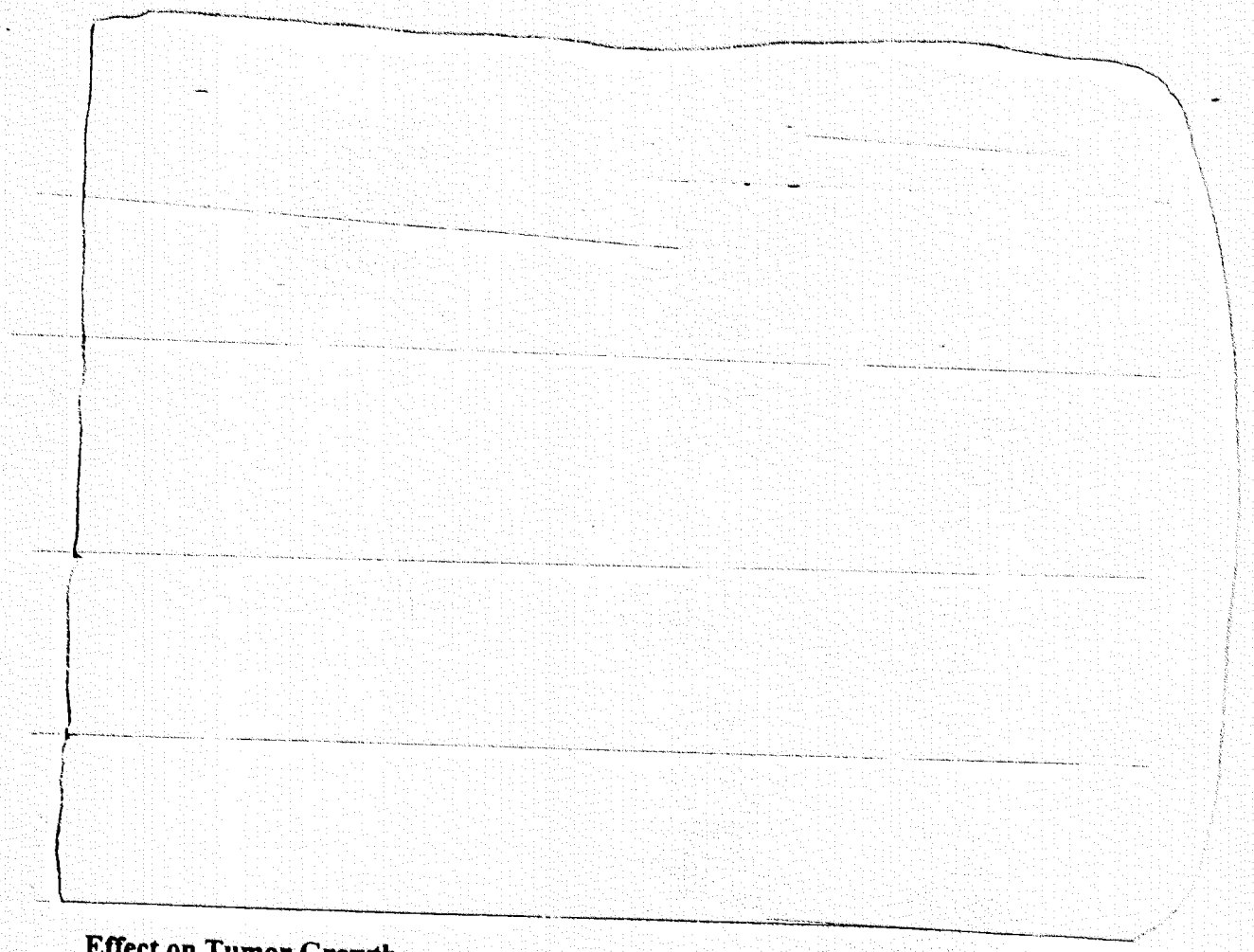
The intra-patient reproducibility of Thyrogen testing with regard to both Tg stimulation and radioiodine imaging has not been studied.

Quality of life of patients was maintained following Thyrogen but was significantly reduced following thyroid hormone withdrawal within four domains assessed by the SF-36 scale. These four domains were: physical functioning, physical role, bodily pain, and emotional role. As expected, Thyrogen administration was not associated with the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal.

Pharmacokinetics
see Biopharm review

Indications and Usage

Contraindications
no changes



Effect on Tumor Growth
delete section

Drug-Drug Interactions
no changes

Carcinogenesis, Mutagenesis, Impairment of Fertility
no changes

Pregnancy Category C
no changes

Nursing Mothers
no changes

Pediatric Use
change to:

Geriatric Use
no changes

Adverse reactions
second paragraph, second line and table heading
Change to

Add the following adverse reactions to the third paragraph which lists those occurring in < 1% of patients:

Add a separate paragraph to the Adverse Reactions section:

Overdosage

Retain the first sentence and replace the second and third sentences with the following:

Dosage and Administration:

The 3 dose regimen should also be included as an option and, therefore, the first sentence should be revised to read:

The recommended scanning time and Tg testing should be changed from [redacted] after the final Thyrogen injection.

/S/

Jean Temeck, M.D.

/S/

5-21-98

/S/

5/22/98

cc. NDA Arch 20898
HFD-510: Dr. Orloff/Mr. McCort
HFD-510: Div. file

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