HYPERTHYROIDISM

Medical Grand Rounds
Parkland Memorial Hospital
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CASE HISTORY

[redacted]. is a 24 year old [redacted] female from [redacted], Texas, who was referred by her physician for evaluation of thyrotoxicosis. Six weeks before admission, she noted increased activity and had no trouble in staying awake for long hours while "cramming" for exams. She noted weakness, an increasing frequency of errors in her work and heat intolerance. Her husband noted her enlarging thyroid gland and a pronounced stare. The patient developed a huge appetite, easily eating more than her husband who was engaged in a considerable amount of manual labor.

She had taken birth control pills until 4 months prior to the onset of symptoms. She had normal periods for 3 months, and spotting during the month in which symptoms developed. She did not have a period for 1 month prior to admission. Three pregnancy tests were negative in the week before admission. Physical examination showed a vivacious, hyperkinetic female with marked lid retraction but no conjunctival swelling and only minimal difficulty in converging the eyes. The thyroid was estimated to be 90 - 100 gm in size and diffusely enlarged. Pelvic examinations by the intern and by an OB resident revealed a normal uterus but a difference of opinion regarding softness of the cervix. A repeat urine test for pregnancy was negative.

Lab studies included a T_4>20μg/100ml, PBI of 16.4, T_3-resin uptake of 48%, a 24 hour RAI of 53% and the scan confirmed diffuse uptake over the gland.

The patient was eager to start a family in the early future so she accepted our recommendation for surgical therapy. She was placed on propanolol, 20mg q.i.d. and PTU, 150mg q.6h. Her pulse dropped to 90 - 100 and she was more comfortable. The patient did not wish to restart BCP and a coil could not be inserted until her next period. The husband was agreeable to using a condom during this period.

The patient was to be followed at [redacted] until the time of surgery. Within 2 weeks she developed increasing morning nausea and vomiting and her pregnancy test became positive.

Her morning sickness continued and was relatively severe. Her PTU was increased to 800mg/d and doses were administered at noon and thereafter in an attempt to control her continuing hyperthyroidism. Her physician indicated the patient was taking most if not all of her medication. By [redacted], it was apparent she was not improving and she was admitted to [redacted] hospital in early [redacted] for observation and therapy. Her nausea was brought under control and she was transferred to [redacted] on [redacted]/73 for continued therapy and preparation for surgery.

At this time, she was found to have twins and her estimated gestation was late mid-trimester. Her T_3 had shown a steady fall after her hospitalization. Her propanolol and phenobarbitol were discontinued on [redacted]/73. On [redacted]/73 she went into premature labor and delivered twins weighing 1330 and 1520gms with Apgar scores of 8→9 and 7→9 respectively.

The patient was LATS negative and the cord bloods for the two children were LATS negative. Their course was relatively normal with some hyperbilirubinemia, a slightly increased pulse in one, but without evidence of a goiter. Their T_4 levels were elevated but subsequently dropped to:

			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]/74
[redacted]	A	T_3 resin	39.5		36.5	28%	-
		T_4	>20	>20	>20	3.0	7.0
[redacted]	B	T_3	32.5	32.5	35.5	30%(25-35)	-
		T_4	20	17.6	15.5	3.8(4.5-11.5)	

One of the twins developed a small goiter after delivery but this subsequently disappeared by discharge.

The patient was subsequently re-admitted and had a subtotal thyroidectomy in [redacted] of 1973. Post operatively she developed hypocalcemia with a value of 7.8 mg/100ml. She was supplemented with oral and IV calcium and was later discharged with a serum Ca in the 8 range. She was started on thyroxin 0.2mg per day and was to be followed by her physician in [redacted].

One month ago, she noted leg and foot cramps, and now notes some fatigue and coldness. A recent serum Ca was 8.2mg/100ml, T_4 was 2.9 g/100ml and T_3 resin was 25% (nl 27-35). She is being started on calcium and Vitamin D supplements for hypoparathyroidism and encouraged to take her thyroxin on a regular basis for hypothyroidism.

This patient exemplifies the problems that can be faced with hyperthyroidism. Dr. Wilson reviewed this topic for grand rounds in 1967. Todays presentation will take a broad view of this topic and concentrate primarily on recent developments in the field.

A. *THYROID PHYSIOLOGY*

The role of TSH and its feedback inhibition by thyroid hormone have been previously identified by indirect means. The recent development of assays for thyrotropin (TSH) and discovery of thyrotropin releasing hormone (TRH) have confirmed and extended this concept. TRH was the first pituitary releasing factor to be isolated and its structure identified. It has served as a prototype for investigation into other releasing factors and therefore has served an even greater role than in thyroid physiology alone. TRH is released from the hypothalmus into the portal system, and stimulates the thyrotroph cells in the anterior pituitary to release TSH. TSH in turn enters the blood stream and stimulates the thyroid follicular cells to synthesize and release hormone. These hormones, in turn, have a negative feedback effect at the hypothalmic and pituitary level. The fact that thyroid hormones will inhibit TRH mediated TSH release is of more than casual interest since the release of TSH following TRH stimulation is increasingly used for evaluation of pituitary reserve. Thus, the test cannot be used on patients already taking thyroid hormones.

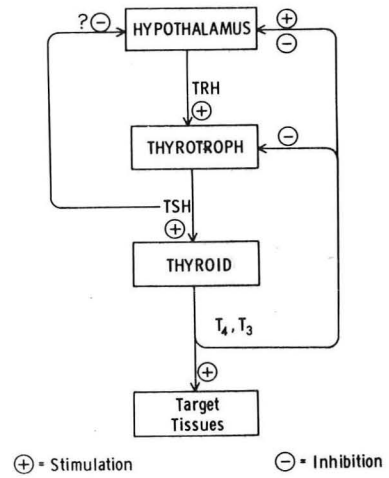
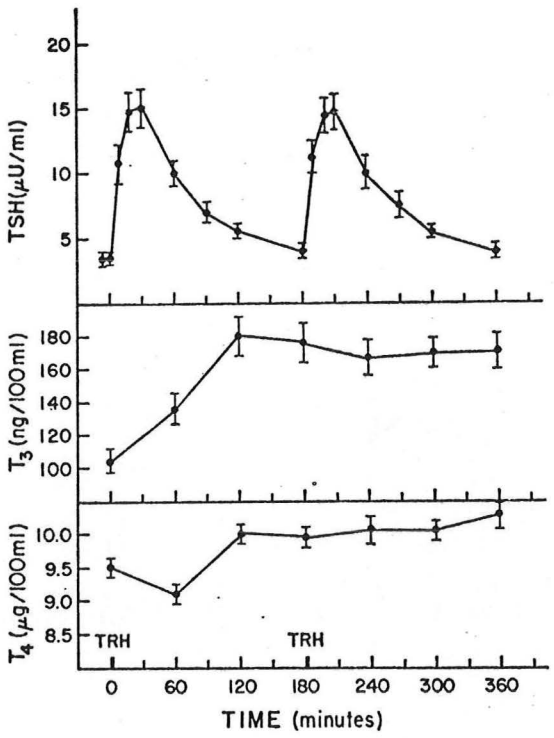


Fig. 1

Figure 2 illustrates the rapid effect of injected TRH upon TSH. Note the rapid rise of triiodothyronine (T_3) within 2 hours of its administration and the slower rise of thyroxin (T_4). This study also demonstrates that it takes longer than 3 hours to develop the previously noted thyroid inhibition of TRH-mediated TSH stimulation.

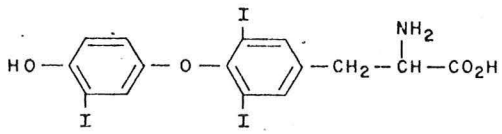
Guillemin, R., et al: Vit. & Horm. 29:1, 1971

Parks, J.S.: J. Clin. Endocr. 37: 466, 1973

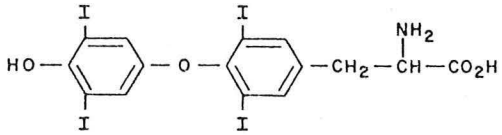


Effects of two consecutive doses of TRH on serum TSH, T_3, and T_4 levels in 15 children with normal endocrine function. Synthetic TRH, 5 μg/kg, was injected at 0 and 180 min. Values are expressed as mean ± SEM.

Fig. 2



3′,3,5— TRIIODOTHYRONINE T_3



THYROXINE T_4

Fig. 3

Considerable controversy has been generated over the relative importance of T_4 and T_3 in human metabolism. The development of competitive binding and radioimmunoassays for T_4 and T_3 have permitted experimental analysis of this problem. Greer has summarized several papers which have demonstrated that there

Greer, M: Mayo Clin. Proc. 47:944, 1972

is a widely varying content and secretion of T_4 and T_3 from the gland depending on the iodine content and metabolic state of the patient.

The T_3/T_4 ratio in the thyroid and plasma increases with iodine depletion, following TSH stimulation and with hyperthyroidism (Graves').

It has been long recognized that there is a greater delay before the onset of the metabolic effects of T_4 than that of T_3. This fact and the greater affinity of T_4 binding to thyroxin binding globulin in the plasma has supported the concept that T_4 might act as a prohormone, having relatively little metabolic activity of its own until it is converted to T_3 in the plasma or at the cellular level. Table 1 is taken from an excellent review by Larsen of several investigators' data concerning T_3 and T_4 metabolism.

Table 1

Current Estimates of Kinetic Parameters for Thyroxine and Triiodothyronine

	Serum Concentration (μg/liter)	Distribution Volume (liter)	Turnover Rate (day-1)	Total Extrathyroidal Hormone (μg)	Metabolic Clearance (μg day-1)	Free Hormone Percent	Free Hormone ng/100 ml
Thyroxine	84.2	9.4	0.100	790	79	0.024	2.0
Triiodothyronine	1.20*	37.3†	0.726†	45	33	0.36‡	0.43

The low plasma levels, larger volume of distribution, rapid turnover rate, metabolic clearance relative to pool size, and relatively high plasma concentration of T_3 all are compatible with its lower affinity to TBG. Since injected T_3 is 4 times more metabolically active than T_4 , the relatively higher concentrations of the free hormone in the plasma support a significant role for T_3 in the body.

Sterling et al (JCI 49:855, 1970) demonstrated evidence for peripheral conversion of T_4 to T_3 in vivo. It now appears that almost 1/3 of T_4 metabolized each day is converted to T_3.

Braverman, L: JCI 52:1010, 1973

This would suggest then that approximately 22μg of the T_3 secreted per day is formed peripherally and 11μg is secreted from the thyroid. The ratio of T_3 and T_4 secretion per day isn't far from the ratio of T_3 to T_4 stored in the thyroid gland.

Chopra, I et al: J. Clin. Endocr. 36:311, 1973

Although these data support an important role for T_3 in peripheral metabolism, they do not indicate the fate of the remainder of secreted T_4. Some of this is broken down via non "metabolic" pathways but the fate of the remainder has not been identified. One possibility is that the T_4 is metabolized to T_3 at the cellular level, performs its metabolic activity, and is further metabolized to di and mono iodo derivatives before re-entering the circulation.

The release of T_4 into the circulation and its plasma concentration throughout the day remain constant (Fig. 4) despite intermittant release of TSH. This is most likely due to the slow turnover of T_4 bound to TBG. Since T_3 is less tightly bound, one might expect greater changes in T_3. This is seen in Figure 5 where one observes a transient but significant rise in plasma T_3 levels into the hyperthyroid range 2 - 8 hours after administration of T_3. This also occurs, to a lesser extent when a combination of T_3 and T_4 are given, but not following T_4 alone (Figure 6)

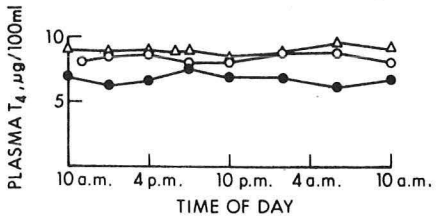


Fig. 4

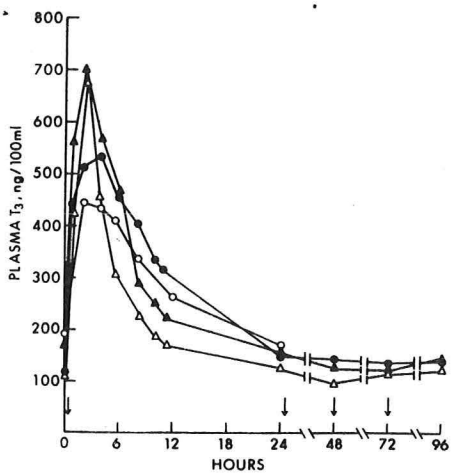


Fig. 5

Surks, M. et al: JCI 51: 3104, 1972

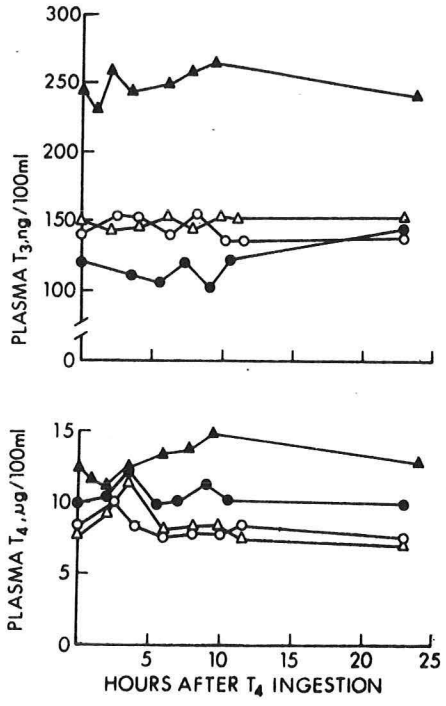


Fig. 6

While this provides a rationale for not using T_3-containing medications as replacement therapy in hypothyroid subjects subject to cardiac arrhythmias, proof of a deleterious effect in normal replacement doses has not been made. At Parkland, we prefer to use an all T_4 preparation which eliminates this potential problem.

Thyroid hormones affect the half life of T_3 and T_4 in humans. The half life of T_3 is reduced to 0.63 days in Graves' disease and increased to 1.38 days in hyperthyroidism. This seems to represent a compensatory mechanism to modify the effects of surplus and deficits of the hormone.

Nicoloff, J et al: JCI 51:473, 1972

Several common pharmacological agents will alter the binding and metabolism of both T_4 and T_3. Aspirin and dilantin,in concentrations that can be attained clinically, will displace T_4 and T_3 from thyroid binding globulin.

Larsen, P: JCI 51:1125, 1972
Oppenheimer, J et al: Endocrinology 71:496, 1962

Phenobarbitol enhances metabolism of the hormones by induction of the microsomal enzymes in normal and hyperthyroid patients.(Fig. 7)

Cavalieri, R et al: JCE 37:308, 1973

Fewer advances have been made in understanding the mechanism of thyroid effects upon subcellular metabolism. Only 3 out of 876 pages in Werners' text were devoted to this subject. I, too, will take the easy way out and not delve further into this topic today.

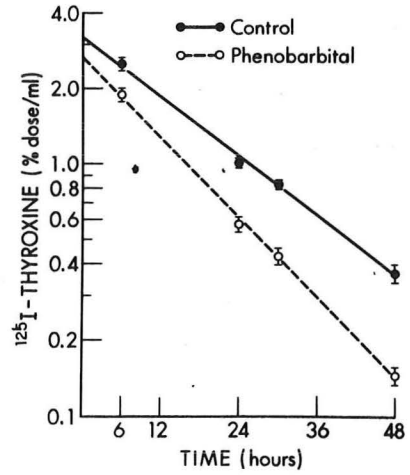


Fig. 7

B. DIFFERENTIAL DIAGNOSIS OF HYPERTHYROIDISM

Table 2: Etiology of Hyperthyroidism

1. Toxic diffuse goiter (Graves')
2. Toxic Uninodular goiter
3. Toxic multinodular goiter
4. Nodular goiter with hyperthyroidism caused by iodine Rx (Jod-Basedow)
5. Tumor secreting TRH or TSH
6. Iatrogenic

Our patient clearly has Graves' disease with a diffusely enlarged, hypersecreting gland and associated mild ophthalmopathy. The other causes may produce some of the symptoms and signs of Graves' disease, but can generally be clearly delineated from it by examination of the patient and obtaining the appropriate laboratory tests.

C. ETIOLOGY OF GRAVES' DISEASE

It is still safe to say that the etiology of this complicated disease is unknown. The earlier concept that excess TSH stimulation might be the cause of hypersecretion of thyroid hormones has been disproven. TSH in Graves' is almost always suppressed to very low values. (Fig. 8)

Hershman, J et al: Annals Int. Med. 74:481, 1971

There are only 3 recorded cases where excessive TSH secretion from a pituitary adenoma has been demonstrated.

Hamilton et al: NEJM 283:1077, 1970

The possibility that Graves' disease is caused by auto immunity is well summarized by Volpe et al (Mayo Clinic 47: 824, 1972). Long acting thyroid stimulation (LATS), identified as an IgG immunoglobin, has been thought by many to play a central role in this disease.

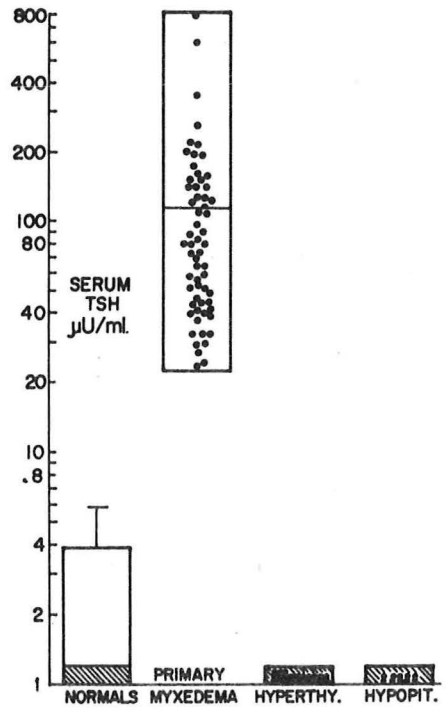


Fig. 8

Table 3—**Some Characteristics of Graves' Disease and of LATS***

Graves' disease	LATS
1. Clinical features pathognomonic†	1. Pathognomonic of Graves' disease†
2. Variable system involvement	2. Relation to number of systems involved
3. Tendency to spontaneous remission	3. Tendency to spontaneous disappearance
4. Favorable response to treatment	4. Tendency to decrease with treatment
5. Neonatal thyrotoxicosis, a placental transmission disease	5. Transmitted across placenta
6. High incidence of various organ antibodies	6. Is an IgG, probably an antibody
7. Familial tendency	7. Familial tendency
8. Diffuse thyroid hyperplasia and universal hyperfunction	8. A general thyroid stimulator, like TSH

Table 3 summarizes the similarity between the occurrence of LATS and various manifestations of Graves' disease.

LATS has been purified and shown to stimulate the thyroid cell in a similar fashion as TSH through the adenyl cyclase system. It still is not clear whether it acts at the same receptor or through an adjacent and different receptor.

Several lines of evidence now suggest that LATS is not the primary cause of the hyperthyroidism. Only 40 - 60% of patients with Graves' disease show a positive LATS assay. Concentration of the plasma to increase the sensitivity of the assay fails to markedly increase this figure.

There has been no correlation of LATS with the severity of the disease, and it can be dissociated from thyroid nonsuppressibility during treatment with anti-thyroid drugs.

Yamashita, K et al: JCI 51:463, 1972

Burke: Am. J. Med. 45:435, 1968

Lipman et al: Am. J. Med. 43:486, 1967

Chopra, I et al: JCE 30:524, 1970

The transplacental passage of LATS from mother to baby with associated neonatal thyrotoxicosis has been used as evidence for the role of LATS in Graves' disease. Exceptions, however, have been noted. Our cases presented today also may be an exception since the mother's and the cord bloods were LATS negative, yet at least one of the babies had a rapid pulse and transient goiter following delivery.

McKenzie: JCE 24:660, 1964

Hollingsworth, et al: J. Pediat. 81:446, 1972

One group recently examined the effect of LATS negative plasma on intracellular colloid production in human thyroid slices. They found 82% of these sera contained a stimulus of thyroid tissue that was not TSH, and was not dose related. Other studies to determine whether this

was a LATS-like material were not reported, so it is premature to speculate whether this represents a more sensitive assay of LATS activity or the effects of a new thyroid stimulator.

Onaga, T et al: JCE 36:859, 1973

Werner et al (NEJM 287:421, 1972) have demonstrated other immunoglobulins (E,M & G) as well as complement in the thyroid connective tissues of patients with Graves' disease. They concluded this was compatible with an autoimmune basis for the disorder, but the multiplicity of the immunoglobulin response dictated against a simplistic role for the 7S IgG LATS.

Ingbar has reviewed the role of iodide in the regulation of thyroid hormonogenesis (Mayo Clin. Proc. 47:814, 1972). He suggests that part of the hypersecretion in Graves' disease is due to loss of the thyroid's ability to control (autoregulate) its own iodine content. There is only indirect evidence to support this concept, but it is provocative and may lead to a better understanding of iodine in thyroid control.

Recently, Volpe and his coworkers have suggested that Graves' disease is a disorder of cell mediated delayed hypersensitivity.

Farid, et al: NEJM 288:1313, 1973
Volpe, et al: Mayo Clin. Proc. 47:824, 1972

They base their conclusions on the same indirect data supporting an immunological abnormality, but suggest that the primary stimulation of the thyroid cell comes from sensitized T cells which arise through mutation and some undefined genetic predisposition.

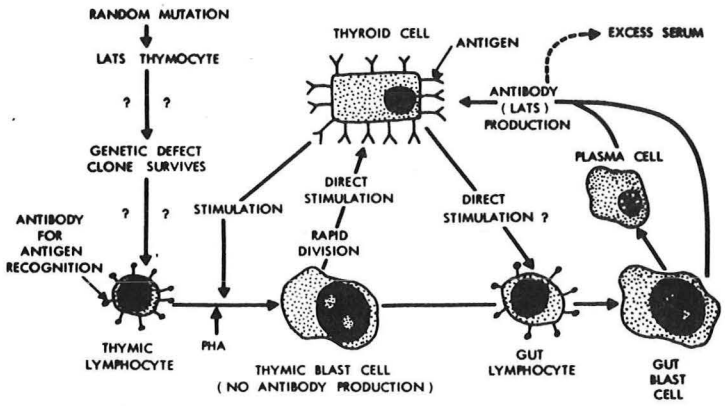


Fig. 9

The proposed defect (Fig. 9) is an inability of the body to clear these unwelcome lymphocytes because of an inherited defect in immunological surveillance. These cells then mature, attack and stimulate the thyroid cell directly. They suggest that these T dependent cells, in some cases, then stimulate the B cells to produce several types of antibodies and including LATS. They have used a technique measuring the production of migration inhibition factor (MIF) by sensitized lymphocytes when exposed to thyroidal antigen as an index of cell mediated immunity(Fig. 10). Inhibition of leukocyte migration by cells from patients with Hashimoto's thyroiditis, a disease commonly believed to be caused by delayed hypersensitivity, was similar to that in patients with Graves' disease. This inhibition by thyroid antigen did not occur in patients with other thyroid disorders such as toxic and nontoxic nodules. They subsequently have reported that the

% of T dependent lymphocytes in patients with Hashimoto's thyroiditis and in those with Graves' disease are higher than in their control subjects. (Fig. 11)

It is of interest that they have observed a return of the T dependent cells to normal in those patients who have gone into remission.

They and others have extended their studies to suggest that a similar deficiency in immunological surveillance against lymphocytes sensitized to retro-orbital tissues occurs in patients with Graves' ophthalmopathy.

Munro, et al: JCE 37:286, 1973
Munro, et al: JCE 34:1090, 1972

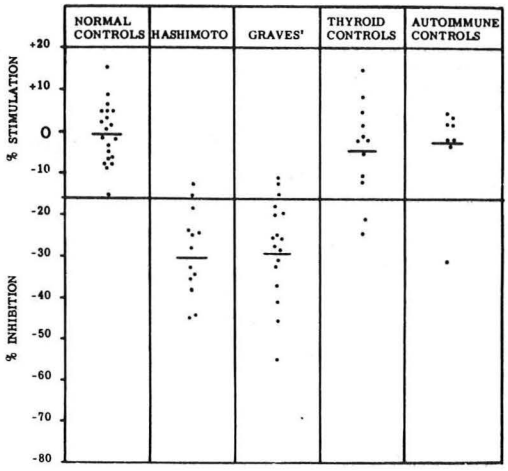


Fig. 10

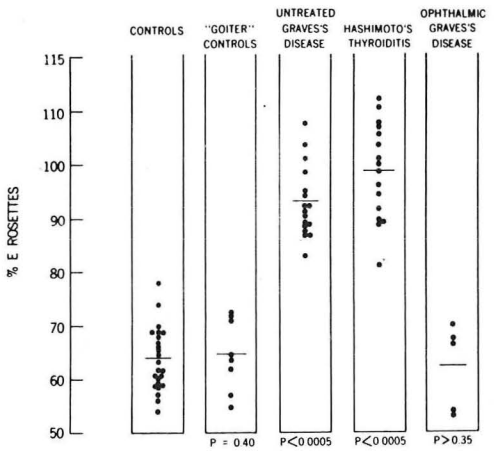


Fig. 11

Kriss has summarized evidence suggesting that the thyroid and eyes share a common lymphatic drainage system which under certain conditions would permit antigens, antibodies, and/or lymphocytes from the thyroid to gain access to the retro-orbital tissues.

Kriss: JCE 31:315, 1970

Kahn et al: J. Biol. Chem. 246: 6570, 1971, however, have demonstrated exophthalmic activity in a fragment of TSH which was devoid of any TSH-like activity. They speculated that in hyper-thyroidism, the TSH production was not really suppressed but rather diverted by intracellular enzymatic metabolism into such a fragment that produces exophthalmus. While this would account for the abnormality developing while circulating TSH was low, it does not account for the reported case of exophthalmus developing in a completely hypophysectomized patient.

Furth, et al: JCE 22:518, 1962.

These studies, though still inconclusive, have opened this field to the immunologist; and we all will have to move rapidly in order to keep up!

D. DIAGNOSIS OF GRAVES' DISEASE

Our patient did not present a diagnostic problem. Her T_4, her T_3-resin test and 24 hour uptake were quite elevated, confirming a diagnosis already apparent at the time of admission.

I would like to comment upon some recent developments in the diagnostic approach to these patients. The use of tests to measure circulating T_3 has already been mentioned. It appears that there is an increase in T_3 relative to T_4 in Graves' disease. At present it is not clear whether there is only a change in T_3 production in the abnormal gland, a change in the metabolism of T_3 and T_4 , or both. As seen in Table 4, there is little if any overlap between T_3 in grossly hyperthyroid and normal subjects. This test, as it becomes clinically available, may help clarify the diagnosis in some subjects with borderline or mildly elevated T_4 concentrations.

Table 4. Serum T3 Determinations In Various Laboratories Using Radioimmunoassay and Competitive Protein-Binding Technique

	Competitive Binding Protein Technique Serum T3 (ng/ml) (mean ± SD)		
Authors	Euthyroid	Hyperthyroid	Hypothyroid
Sterling et al.[6]	2.20±0.27	7.52±2.82	0.98±0.48
Wahner and Gorman[10]	2.43±0.40	6.71±2.53	1.87±0.92
Larsen[11]	1.8 ±0.4	6.7 ±3.3	0.66±0.39
Dussault, Lam, Fisher[12]	0.98±0.48	4.43±0.51	U*(0.25)
	Radioimmunoassay		
Gharib, Mayberry and Ryan[15]	2.18±0.55	7.60±2.89	1.03±0.43
Chopra, Solomon, and Beall[18]	<1.00 – 1.70	<1.00 – 13.00	U*(1.00)
Mitsuma et al.[21]	1.38±0.23	4.94±2.65	0.62±0.09
Lieblich and Utiger[22]	1.45±0.25	4.29±1.46	0.99±0.24
Snyder and Utiger[23]	1.02	—	—
Larsen[24]	1.10±0.25	5.46±4.42	0.39±0.21

*Undetectable.

Mitsuma, T et al: Rec. Prog. Horm. Res. 26: 249, 1970

Sterling, K: Rec. Prog. Horm. Res. 26:249, 1970

Larsen, P: Metab. 21: 1073, 1972

Sterling, et al, demonstrated that some clinically hyperthyroid subjects may have elevated plasma T_3 concentrations and normal or subnormal T_4 concentrations. The entity, now called T_3 toxicosis, has explained the variance between symptoms and biochemical analysis in some patients, but has opened up new questions. While it has been reported most frequently in toxic adenomas, several patients with diffuse enlargement have now been described. There are some patients with elevated T_3 concentrations and normal T_4 levels who do not appear clinically to have thyrotoxicosis. The T_3/T_4 ratio is often elevated following isotopic and even surgical therapy of Graves' disease, and also in hypothyroid states. It appears that this assay like most others will require careful evaluation in its clinical setting.

It is important to emphasize that this test is not available at the present time in this institution.

The T_4 test, assayed by competitive binding and often referred to as T_4 Murphy Pattee, has become popular and for very good reasons. It is not altered by iodide contamination from dietary intake or by contrast media. It can be performed rapidly and is replacing the PBI as the preferred thyroid screening test. However, it is altered by increases in thyroid binding globulin induced by the intake of estrogens in anovulatory compounds, post menopausal medications and by pregnancy. The effect of pregnancy on the circulating T_3 T_4 and TBG is seen in Figure 12. These increases can be seen after the first month of gestation.

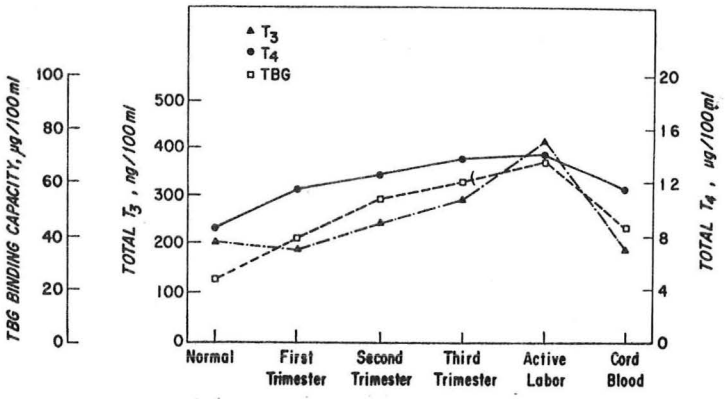


Fig. 12

It is under these circumstances that the reciprocal decrease in the T_3-resin test is helpful for diagnostic purposes. The T_3-resin test, which is universally available, should not be confused with the above mentioned assay of circulating T_3. This T_3-resin name is very confusing since it does not measure T_3 at all, but is rather an indirect assay of thyroxin binding globulin in the plasma. Ratios of the T_4 and T_3-resin tests, usually called an *index*, have been utilized to express these reciprocal changes as a single number. Because of inherent inaccuracies of the T_3-resin test, we have not found the index any more helpful than separate evaluation of the two tests. The multiplicity of names, and the fact that some suggest that they represent a direct assay of free T_4 or T_3 rather than an estimate based on an indirect and relatively inaccurate assay of TBG leads to confusion in interpretation.

Fisher, D: J. of Pediat. 82:1, 1973

Becker, et al: Mayo Clin. Proc. 47:835, 1972

Harvey,: Lancet, p.230, July 31, 1971

Souma, J: Amer. J. Obstet. Gyn. 116:905, 1973

The TSH assay might be of help in certain cases of borderline hyperthyroidism. It is suppressed to low or undetectable levels in Graves' disease, so an elevated or high normal value might clearly rule out (see Fig. 8) Graves' disease. We rarely have used it for this purpose.

The RAI-24 hour uptake test has been helpful, but criteria for normal are now in question since there has been a dramatic increase in iodine added to table salt, bread, and many other food stuffs. This has lowered the normal range in many areas to a 24 hour value of 5 - 30% rather than

10 - 15 to 45%. It still has diagnostic value for questionable cases of hyperthyroidism, especially when combined with T_3 suppression

Pitman, et al: NEJM 280:1431, 1969

Oddie, et al: JCE 30:659, 1970

Some other tests may become useful in the diagnosis of hyperthyroidism over the next few years. Direct determinations of the unbound (free) T_4 and T_3, available in some research and large diagnostic laboratories, may help determine whether the active, unbound hormone is indeed increased as compared to total T_4 or T_3. These studies are difficult to perform and values reported in some of the commercial labs remain suspect.

Assay of TBG by radioimmunoassay might be of help in interpreting the standard thyroid tests. Since reciprocal changes of TBG occur in hyper and hypothyroidism, this direct assay would be more specific than the indirect assay with the T_3-resin test. Circulating thyroglobulin often parallels that of T_4.

Van Herle, A, et al: JCI 52:1320, 1973

The overlap of values in patients with thyroiditis without hyperthyroidism and patients with Graves' disease, as well as its non-availability will restrict its value.

E. THERAPY OF HYPERTHYROIDISM

This discussion will be divided into two sections, one dealing with (1) short-term - symptomatic treatment and the second with (2) long-term therapy and its sequelae.

1. Short term - symptomatic treatment

Todays patient was hyperkinetic and quite uncomfortable. We felt she would benefit from symptomatic treatment while awaiting the effects of definitive long-term therapy. Earlier studies have already demonstrated an effect of agents which decrease sympathetic activity upon the symptoms of hyperthyroidism.

Lee, et al: JCE 22:879, 1962 (guanethidine)

Waldstein, et al: JAMA 189:609, 1964 (guanethidine)

Canary, et al: NEJM 257:435, 1957 (Reserpine)

Theilen, et al: Metabolism 12:625, 1963 (alpha methyl dopa)

It is occasionally difficult to adjust the dosage of these drugs because of their slow onset of action, persistent drug levels, and annoying side effects. This has led to the introduction of agents that rapidly block

the β receptor. Several uncontrolled reports have enthusiastically utilized propanolol as adjunctive treatment of the syndrome.

The bulk of evidence from controlled studies of propanolol indicate that it improves the subjective symptoms and signs of hyperthyroidism.

Table 5: Effect of β adrenergic blockade in thyrotoxicosis

Palpitation	↓
Tremor	↓
Heart Rate	↓
Lid Lag	↓
Hyper-reflexia	↓
Subjective improvement	↑

Marsden, et al: Acta. Endocr. 57:353, 1968

Shanks, et al: Lancet, P. 973, 17 May, 1969

Grossman, et al: Annals Int. Med. 74:875, 1971

Maximov, et al: Circulation 45 & 46:11-190, 1972 (Abst.)

It should be emphasized that while these studies compared the effect of β blockade with either placebo or no therapy, the agents previously mentioned, sedation and bed rest alone can affect some or much improvement in these symptoms and signs. It seems apparent however, that these symptoms are mediated in part by β adrenergic activity, since blockade will decrease the hyperactivity but will not reduce it to normal. It should be emphasized that these agents, with the exception of phenobarbital, have no effect on the underlying thyroid hypersecretion. Phenobarbital may decrease plasma concentrations by enhancing its metabolism as we noted earlier.

There is a significant effect of the β blocking agents on the cardiovascular system.

The hemodynamic changes, seen in Table 6, indicate that intravenous propanolol will decrease the hyperdynamic state.

Table 6: Summary of Hemodynamic changes following β adrenergic blockade

Heart Rate	↓	Mean Arterial Pressure	NC
Cardiac Output	↓	Left Vent. End Diastolic Pressure	NC
Max. dp/dt	↓		
Left Vent. Work	↓		
Left Vent. Stroke Power	↓		
Mean system Ejection Rate	↓		

Pietras, et al: Arch, Int. Med. 129:426, 1972

Wiener, et al: Amer. J. Med. 46:227, 1969

There are three consequences of β adrenergic blockade that are of concern. (1) Propanolol should not be given to patients with asthma, (2) it should be given with care in diabetic patients on medications since it may inhibit the normal glycolytic response to drug induced hypoglycemia, and (3) the possibility that congestive heart failure might be induced or worsened by eliminating the β adrenergic mediated inotropic effects on the heart.

Most of this concern has been extrapolated from the many published cases of CHF precipitated in patients with primary heart disease treated with intravenous or high oral doses of β blocking agents or guanethadine,

Gaffney, T, et al: Amer. J. Med. 34:320, 1963

but cases have been reported in thyrotoxic patients (see Maximov above) and one local patient possibly went into congestive heart failure while on propanolol. While it is not clear in these individual instances that propanolol blockade of the β mediated inotropic effects tipped these patients into CHF as compared to the natural course of the underlying disease and an already decompensated heart, it is obvious that this agent should not be used unless the potential improvement outweighs the probable side effects.

Thus, a patient with a supraventricular arrhythmia treatable by propanolol and in mild congestive heart failure might benefit more by control of the arrhythmia than by a small loss in contractility. Patients with evidence for cardiac ischemia and with a rapid heart rate will also likely benefit from this therapy. Patients with evidence for a primary myocardial disease probably should not be treated unless other indications for propanolol treatment are present.

I feel the following recommendations would help avoid such problems.

Propanolol in Hyperthyroidism

1. Do not use if the patient is <u>not</u> really in need of symptomatic relief.
2. <u>Evaluate</u> the patient thoroughly for contraindications to therapy (You should do this anyway)
3. <u>Evaluate</u> the cardio-vascular system for decompensation.
4. Start with <u>low</u> oral doses of the agent since a response often is noticeable in 4 - 6 hours. Thus, I often start a patient at 10mg q.i.d. and increase the dose by 40mg/d depending on the patient's subjective and objective response.
5. <u>Avoid</u> IV dosage
6. <u>Re-evaluate</u> the patient after starting therapy and before increasing the dosage.
7. Do not use prolonged therapy without <u>reassessing</u> its need.

I have not discussed the use of propanolol in thyroid storm, since this is a complex and specialized form of treatment which has not been compared to the current effective management of iodide, reserpine, steroids, and adjunctive therapy. I am enclosing the following 3 articles for your evaluation of the use of these agents in thyroid storm.

Mazzaferri, et al: Arch. Int. Med. 124:684, 1969 (Guanethidine)

Das, et al: Ann. Int. Med. 70:985, 1969 (Propanolol)

Dillon, et al: NEJM 283:1020, 1970 (Reserpine)

2. Long-term therapy and its sequelae

The long term therapy of Graves' disease has consisted of surgery after medical control of the hyperthyroidism, medical control alone, and administration of radio-isotopes. This is a broad field that cannot be covered in detail today, but the following references may be of help.

Mayo Clinic Proc. 47 #11:835, 1972

Mayo Clinic Proc. 47 #12: 953,962,966, 1972

Seminars in Nuclear Med. 1: Oct., 1971

a. Radio-isotopes

The use of radio-isotopes for control of thyrotoxicosis has increased dramatically since the late 1940's, The advantages of this type of therapy are obvious, and have led to its widespread use. These include a fairly rapid response to therapy, it can be done as an outpatient, it is a non-surgical procedure that can be repeated as necessary and it produces a high degree of control of hyperthyroidism.

It has become apparent over that years that this control is through destruction of the thyroid cells, rather than some change in the internal or external control mechanism operative in Graves' disease. This cell destruction is primarily mediated via the β energy of ^{131}I rather than the gamma rays and remission occurs generally 4 - 8 weeks after therapy. The radiation damage to the remaining cells is manifest at a later period when mitoses should occur. The cells are incapable of dividing and eventually die. This leads to the now well recognized sequelae of hypothyroidism.

The possibility of genetic damage to the patient has restricted the use of ^{131}I in children, although it has been used under certain circumstances when other modes of therapy are not feasible.

Hazek, A et al: NEJM 283:949, 1970

Goldsmith, R: Mayo Clin. Proc. 47:953, 1972

Amenorrhea and oligomenorrhea are frequently seen in hyperthyroidism. In our patient, the 3 negative urinary pregnancy tests and the pelvic examinations led us to conclude that she was not pregnant. She was subsequently given 100μCi of ^{131}I for a 24 hour uptake and scan. A decision subsequently was made not to treat her with therapeutic doses of RAI since she wished to have children in the next 1 - 2 years and was fairly young.

To our chagrin, the patient was or shortly thereafter became pregnant. A dose of 100μCi for her scan will give an estimated dose of 0.2 - 0.3 rads (2.3 mrad/μCi) exposure to the ovaries. A slightly higher concentration of I^- in the fetal circulation than in the maternal circulation might give a greater exposure, depending on the time of implantation. Since the fetal tissue is particularly sensitive to radiation during the first trimester, we assumed that she was indeed pregnant at the time she received the dosage. She would have been pregnant for 1½ months if we assume the estimated fetal age at the time of delivery was correct.

Dr. Gaulden in this institution has reviewed what little data are available from animal and human exposures and currently recommends that the likelihood of fetal abnormalities is remote with exposures of less than 1 rad. For exposures of 1 rad to 10 rads, she feels that the odds are still greatly against a gross fetal malformation, but for exposures >10 rads, the frequency increases significantly.

These data are best summarized in her lecture #9, March 7, 1974, for the radiation biology course for radiology residents.

Other references include:

Dalrymple, Gaulden, et al: Med. Radiation Biology, W. B. Saunders, 1973

Einhorn, et al: Acta. Radiol. (Ther.) Stockholm 11:193, 1972

Sternberg, J: Diagnosis and Treatment of Deposited Radionuclides, Excerpta Med. Fndn. Symposium held at Richland, Wash. May 15, 1967

The effect of radiation from ^{131}I therapy of hyperthyroidism on the subsequent development of leukemia and cancer has been hotly debated. Studies by Pochin published in 1960 were based on public health data and physicians reports. They found no increase in the rate of leukemia on an age and sex adjusted basis.

This study in countries where approximately 60,000 patients had been treated with RAI demonstrated a slightly higher % of patients with acute leukemia than that expected in their population, but this frequency difference was of borderline significance and they did not arrive at a firm conclusion.

Pochin, E: Brit. Med. J. 2:1545, 1960.

Thirty-six thousand patients have been recently evaluated in the Cooperative Thyrotoxicosis Therapy Follow-up Study sponsored by the NIH.

Tompkins, E: AEC Symposium Series #20, Medical Radionuclides: Radiation Dose and Effects, United States Atomic Energy Commission, 1970

Svenger, et al: JAMA 205:855, 1968 (Prelim. report)

This study found no difference in the incidence of leukemia between age and sex adjusted patients having surgery and those having radio iodine treatment alone.

Table 7 NUMBER OF CASES OF LEUKEMIA EXPECTED AND OBSERVED BY CHRONICITY AND CELL TYPE

	Radiation		Surgery	
	Expected	Observed	Expected	Observed
All acute leukemias	7.9	10	6.3	6
Chronic lymphocytic leukemia	4.8	2	3.6	5
All other chronic leukemias	2.7	3	2.2	3
Total	15.4	15	12.1	14

The role of early childhood radiation to the thyroid gland in producing thyroid nodules and carcinoma is now well recognized. The effect of radiation in adult glands has not been fully determined and only a few cases of carcinoma have been diagnosed following such therapy. There have been 30 malignant neoplasms reported following therapy in the Cooperative Thyrotoxicosis Study - an incidence not different from that found in surgically treated Graves'disease.

Hamburger, J: Arch. Surg. 103:762, 1971

Shapiro, S et al: Cancer 26:1261, 1970

A recent summary of other cases, some occurring 10 - 20 years after exposure has emphasized the latency between exposure and disease in the childhood cases and suggests that we might see an increase in thyroidal carcinoma in adults treated with isotopes.

Table 8

Thyroid Cancer After ^{131}I Therapy for Hyperthyroidism

Documented Case Reports	Age (yr) at Time of ^{131}I Therapy	Original Dose of ^{131}I Prescribed, millicuries	Latent Period (yr) Before Carcinoma Diagnosis
Kilpatrick et al: *Q J Med* 26:209, 1957.	60	...	0.25
Sheline et al: *J Clin Endocrinol Metab* 22:8, 1962.	9	5.4	8
Karlan et al: *Calif Med* 101:195, 1964.	11	1.25	2
Kogut et al: *N Eng J Med* 272:217, 1965.	7	...	5
Staffurth: *Br J Radiol* 39:471, 1966.	64	13.5	6
Burke et al: *JAMA* 199:247, 1967.	26	6.7	10
Baker: *Cancer* 23:885, 1969.	52	9.0	12
Barnard and Parsons: *J Neurol Sci* 8:299, 1969.	68	5.0	1
Stamler et al: *J Iowa Med Soc* 60:16, 1970	25	3.4	10
Lima et al: *J Nucl Med* 11:46, 1970.	32	9.0	4
Shapiro et al: *Cancer* 26:1261, 1970.	43	3.0	1.3
Hamburger and Meier: *Arch Surg* 103:762, 1971.	58	30.0	3.75
McDougall et al: *J Clin Endocrinol Metab* 33:287, 1971.	60	12.5	12
Reeve et al: *Med J Aust* 1:993, 1973.	64	12.98	6
Kreps et al: *JAMA* 226:774, 1973.	16	3.2	20

McDougall, I: JAMA 227:438, 1974

At this point, I would summarize our literature as inconclusive. The evidence at hand suggests that the problem of gross somatic sequelae is relatively small, but possibly still significant. On the other hand, there is no assurance that the future genetic consequences will or will not be realized. The persistence of chromosonal abnormalities in RAI treated patients is disturbing.

Nofal et al: J. Nuclear Med. 5:840, 1964

Cantolino et al: NEJM 275:739, 1966

b. Anti thyroid drugs

The use of thionamide drugs such as propylthiouracil (PTU) and methimazole (Tapazole) has been popular since their introduction in the 1940's. Their exact mechanism is still unknown. It appers they do not remove the underlying abnormality in Graves' disease, but rather interfere with the synthesis of thyroid hormones at the organification step. Thus, their administration does not block release of preformed hormone. This partly accounts for the 1 - 3 week delay in therapeutic response while the circulating and stored thyroid hormone are metabolized and cleared. PTU additionally blocks peripheral conversion of T_4 to T_3, suggesting that it may provide a more rapid clinical response than drugs not having this effect.

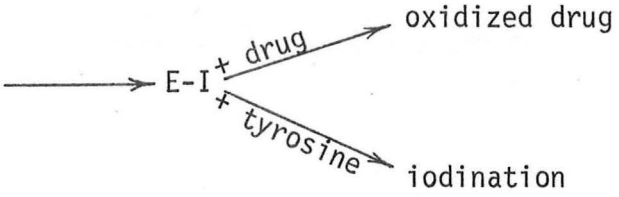
Oppenheimer, J: JCI 51:2493, 1972

It is well accepted that 50 - 60% of patients treated with these drugs will go into permanent remission, and the use of thionamide drugs is encouraged here as in many institutions. This success rate was not obtained during my three years in the service (1968-71) nor have I seen it in observing the results of such treatment in patients at Parkland Hospital and the Endocrine Clinic.

There are several reasons that this might occur. Dr. Taurog has developed evidence that these drugs, in high doses, interfere with thyroid peroxidase organification by inhibiting formation of the enzyme iodine complex.

$$E + I + H_2O_2 \xrightarrow[\text{Drug}]{} E\text{-}I$$

Lower concentrations do not completely inactivate the peroxidose which then oxidizes the drug, reducing its effect even further while continuing to iodinate the tyrosyl moiety.



Increasing the tissue concentrations of the drug will reblock the peroxidose. High concentrations of I^- in the incubation medium interestingly interfere with the drug induced inhibition of the peroxidose.

For many years it has been recognized that an increased iodine intake can precipitate or reactivate quiescent Graves' disease. This has been known as the Jod Basedow phenomenon and is likely related to alteration in intracellular Iodide control mechanisms. Although Iodide ingestion can acutely decrease hormone release in active Graves' disease, long term iodide decreases the remission rate during thionamide drug therapy.

Astwood, E.B: Thyrotoxicosis, 1968, p. 85, (Monograph)

A recent paper by Wartofsky has noted a remission rate of only 14% in patients who were considered reliable while taking thionamide drugs. These authors reviewed the literature and noted a decrease in the remission rates (Fig. 13) reported in some recent studies of the oral agents. They suggested this decrease in the remission rate might be related to the previously mentioned increase in iodine intake in the United States since the early 1960's. It is of note that two studies with relatively higher remission rates published in the late 1960's were from areas in Europe, where iodine intake is less than 1/3 of that in the area of Wartofsky's.

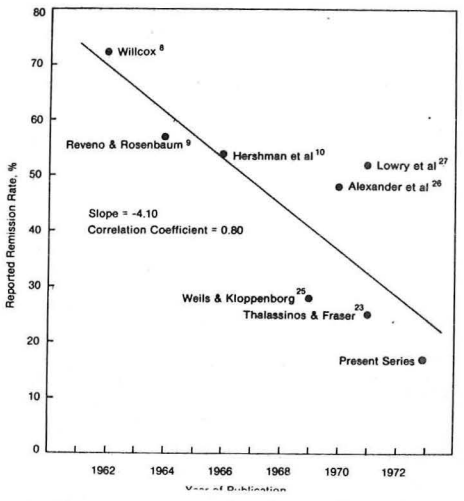


Fig. 13

Wartofsky: JAMA 226:1083, 1973

The problem of long term therapy with a short lived medication makes this a situation susceptable to patient non-compliance. We were concerned because our patient failed to respond to large doses of PTU. Her subsequent and fairly dramatic improvement after hospitalization indicates that her vomiting and compliance associated with pregnancy were preventing adequate drug levels from being achieved.

Since RAI therapy was contraindicated in this patient, the choice was between PTU therapy and surgery. Advocates of each have heatedly debated the advantages and disadvantages of thionamide therapy in pregnancy. The chief disadvantage is that these drugs easily cross the placenta and inhibit fetal thyroid function. This leads to fetal hypothyroidism since there is evidence that T_4 does not readily cross the placental membrane and only small amounts of T_3 do so. Fetal goiter and prenatal or premature births and other fetal abnormalities are reportedly increased following PTU therapy when compared to surgery. This issue is clouded since most studies showing fetal thyroid abnormalities were giving high doses of iodides at some time during the pregnancy in conjunction with the thionamide drug. The iodides alone can have such an effect on fetal thyroid function. Further, most studies have not truly randomized the patient into medical and surgically treated patients. They often compare their particular groups response to that reported by others, or utilize another group of patients not identical to their own.

Herbst, A et al: NEJM 273:627, 1965

Burrow, G: J. Clin. Endocr. 25:403, 1965

Talbert, L et al: Obst. & Gyn. 36:779, 1970

At the present time, there is no evidence that treating the patient concomittantly with thyroid and PTU will alleviate the fetal hypothyroidism. The studies by Larsen (Fig. 14) indicate that the fetal total and free T_3 levels are actually lower than the maternal levels which suggests there is little placental transfer. Fetal TSH is higher than the maternal values until shortly after birth. A rise in T_4 and T_3 to greater than normal values occurs by 2 hours and persists through 48 hours. (Fig. 15)

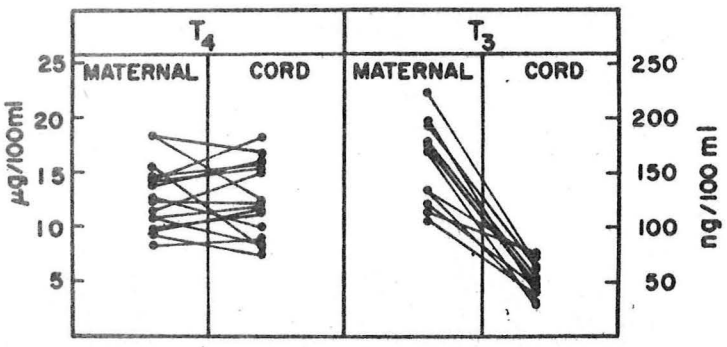


Fig. 14

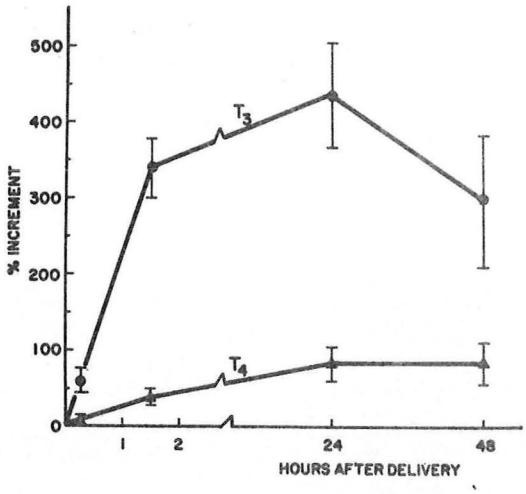


Fig. 15

We anticipated surgery on our patient during the mid-trimester, but the delay in achieving a euthyroid state brought us to the point of considering that the increasing risk of premature birth following surgery was greater than the risk of continued low dose PTU therapy. The patient's spontaneous delivery made this a moot question.

Her subsequent course brings into focus the problems that require follow-up of all hyperthyroid patients. She developed hypocalcemia following surgery with serum calcium values down to 7.8mg/100ml. This subsequently rose to 8.4mg/100ml - and we felt it might return to normal after the drain on her Ca stores was discontinued.

She subsequently has noted muscle cramps and her serum Ca is 8.2mg/100ml 5 months after surgery. Her T_4 is 2.4µg/100ml and T_3 resin test is 25% (normal 27 - 35%)

The incidence of hypothyroidism following surgery or isotope therapy in the Cooperative Thyrotoxicosis Study is shown in Fig. 16.

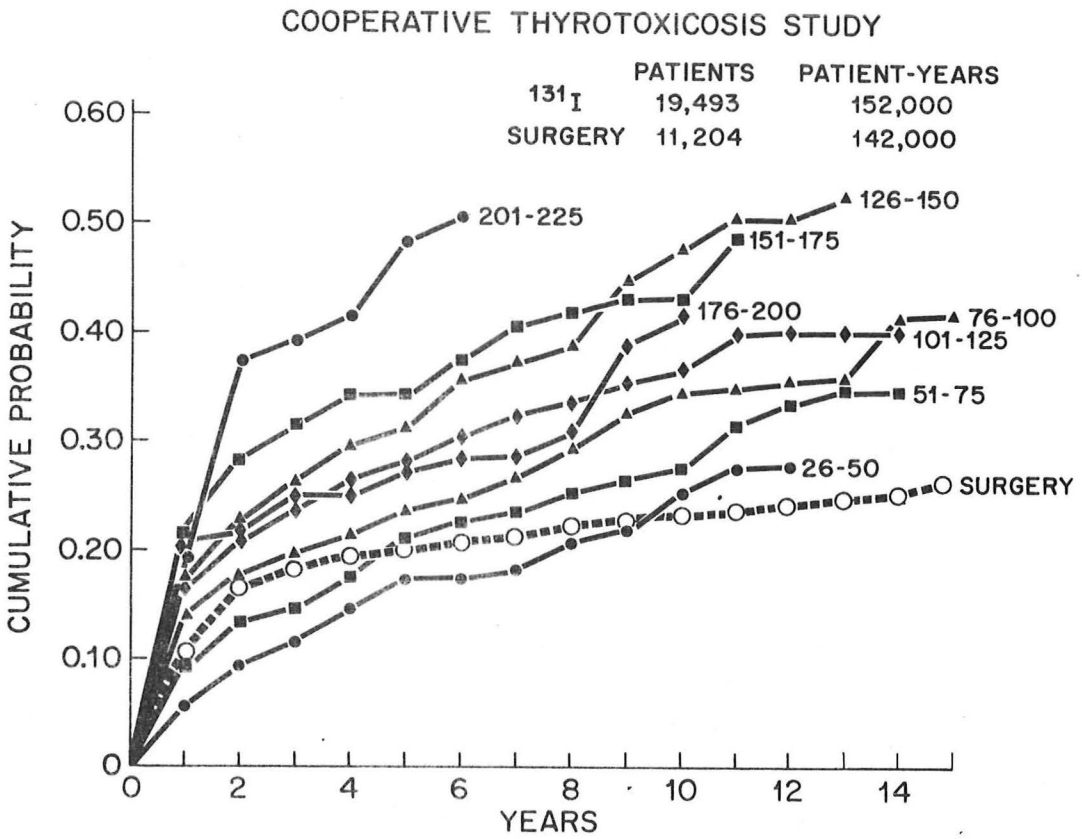


Fig. 16

The values at the end of each curve are the estimated ^{131}I dosage delivered to the gland in µCi/g of tissue. The cumulative probability of developing hypothyroidism after 10 years was 35% for radioiodine and 22% for surgery. Two points should be emphasized.

The influence of decreasing the dosage was seen only in a decreased incidence of hypothyroidism during the 1st year. The incidence of hypothyroidism for the various dosages then increases in a parallel fashion. The incidence of hypothyroidism following surgery is significant and higher than reported in the early literature where follow-ups were not emphasized. Two recent reports suggest the incidence of hypothyroidism after surgery may approximate that after radio-iodine therapy.

As fewer operations are performed, one can anticipate a loss of technical expertise and an increase in morbidity following such therapy, especially in training institutions.

Hedley, A et al: Br. Med. J. 1:519, 1970

Michie, W et al: Br. Med. J. 1:1317, 1972

Parfitt, A: Med. J. Aust. 1:1103, 1971

I would briefly like to mention several relatively recent approaches to therapy of Graves' disease which may be of value in the future. If an easily performed and readily available technique were available to determine when a patient goes into remission on thionamide therapy, then the prolonged therapy in some patients could be shortened, and other patients who show no evidence of remission after an arbitrary period of time might be transferred to another treatment.

Alexander and his group in Glasgow have shown that thyroid suppressibility is a good means of predicting remission. If Volpe's data showing a return of the elevated per cent of T dependent lymphocytes to normal in remission is correct, this in vitro test could be substituted and serve as such an indicator.

Alexander, W: J. Clin. Endocr. 30:540, 1970

Another approach to improving thionamide therapy is to utilize less frequent dosage during the day to improve patient compliance. This does not avoid the problem of increased resistance to drug therapy, and the experience at the VA here was not impressive in terms of control of the disease.

Several groups have used ^{125}I rather than ^{131}I. This isotope has a weaker β energy and theoretically delivers most of its radiation to the cytoplasm rather than the nucleus and it was hoped that it might decrease the incidence of hypothyroidism. This has not been the case in the few published studies.

Lewitus, Z et al: Sem. in Nuclear Med. 1:411, 1971

Temple et al, have shown that treatment of thyrotoxicosis with lithium carbonate inhibits release of thyroid hormone without interfering with thyroid function tests. This effect may be prolonged, especially

when it is combined with a thionamide. When this agent becomes available for clinical use, it may bring patients under control more quickly and shorten the preparation time for surgery. Lithium itself does not alter the underlying disease process.

Temple, R et al: JCI 51:2746, 1972

Finally, I should like to review the Parkland Hospital experience with these 3 approaches to therapy. I was interested in trying to document our impression that we were achieving a less than optimal remission rate with the thionamide drugs.

Dr. Donald Crumbo and Carol Fairchild, RN, have greatly assisted me in a study of 50 consecutive patients with Graves' disease diagnosed from 1968 - 72. Each chart was reviewed, the diagnosis was established, and primary and secondary modes of therapy were identified. Duration of follow-up and degree of control were noted, and the clinical course of each patient was recorded.

Table 9 shows the number of patients in each designated primary treatment group. If the primary treatment for a patient was to be RAI or surgery, but only after thionamide therapy, he was entered in the appropriate primary treatment group and not in the PTU group.

TABLE 9

Follow-up of 50 Treated Hyperthyroid Patients

	n	Lost	Adeq.	2 yrs.
PTU	25	7	18	13
RAI	21	8	13	12
Surgery	4	1	3	2

The number "lost" refers to patients leaving without notice or not returning for appointments before their condition had stabilized. Those listed under "adequate" had been followed long enough to have a stabilized course, were in remission or were already hypothyroid and on replacement medication before leaving. The per cent lost from each group were similar.

The therapeutic course of each group is seen in Table 10. There were only 2 out of 25 patients in the PTU group who went on to spontaneous remission. For a variety of reasons, 18 later were treated with RAI and 5 went to surgery. I would like to emphasize that these patients, to the best of our knowledge in reviewing their charts, were

TABLE 10

	n	Remission	PTU	RAI	Surg.	Lost
PTU	25	2 (8%)	-	18	5	-
RAI	21	18 (86%) .	1	-	-	2
Surgery	4	3 (75%)	1	-	-	-

originally destined to have continuing rather than interim PTU therapy. In contrast, 18 out of 21 patients treated with RAI became euthyroid. Two of the 3 "non-responders" were lost to follow-up before a response could be noted. Nine of the 18 patients who went into remission subsequently were diagnosed as hypothyroid and have been placed on thyroid replacement. Three of the 4 surgical patients were "cured" of their Graves' disease. None of this small group became hypothyroid.

TABLE 11

Cause of Treatment Failure in PTU Group

Failure to take drugs	3
Side effects of drugs	6
Persistence of Hyperthyroidism	8
Recurrence after remission	1
Surgery for goiter (obstr.)	5
	23

Table 11 lists the cause of treatment failure in the PTU group. The major reasons were side effects of the drugs and an inability to control the patient's hyperthyroidism despite pushing the medication to 600mg/d or greater. An attempt was made to identify those patients not taking their medications, but it is certainly possible, if not likely, that this might be a factor in the "persistence" group.

TABLE 12

Side Effects of PTU

Total 38 patients

Leukopenia WBC <3000	6
Skin Rash	2
Abnormal Liver Function Tests	3
Serum Sickness Syndrome	1
Pruritus	1

Table 12 indicates side effects attributed to PTU and which led to discontinuance of therapy in 6 cases. There was a surprisingly high incidence of leukopenia. There were no cases of life threatening agranulocytosis, but one had a pharyngitis and fever associated with a low granulocyte count. A relatively low WBC is not uncommon

in hyperthyroidism and leukocytes may be suppressed from PTU without representing the hypersensitivity reaction that produces agranulocytosis. While this group may represent a portion of physicians' error, it still represents an underlying concern that was strong enough to change the course of therapy.

It is apparent that if this sampling is representative of our recent experience with Graves' disease, we need to re-evaluate our treatment and follow-up programs. The following observations seem valid:

1. We currently have an unacceptably high drop out rate early in the follow-up period. This probably represents problems in in patient education, changing physicians, and patient dissatisfaction with recurrent long vigils in the clinic and pharmacy.

2. There appears to be difficulty in controlling the hyperthyroidism in some patients with PTU.

3. This latter observation is compatible with the observations of Wartofsky and could be due to increased iodide intake; but non-compliance or inadequate dosage recommendations by the physician could also account for these results.

4. We are currently in a therapeutic dilemma; trying to balance (1) relative risks of persistent disease and the likely eventual need for RAI or surgery following PTU treatment, with (2) the probability of hypothyroidism and potential radiation damage following RAI therapy and (3) the risk, morbidity, and slightly lower probability of hypothyroidism following surgery.

I can only conclude that each patient will require a decision based upon individual needs, circumstances, and the probabilities of successful therapy and follow-up. I would suggest that a central follow-up authority be established, similar to the tumor board, in order to coordinate the various clinics evaluating and following these patients.