MEDICAL GRAND ROUNDS

Daniel W. Foster, M.D. April 13, 1978

THYROID STORM

CASE REPORT: G. V. (PMH #62-85-54)

This 53 year old white woman was admitted to Parkland Memorial Hospital on January 30, 1978 with the chief complaint of diarrhea of one day's duration. A few hours prior to admission the stools had become black and sticky. On arrival at the Emergency Room the stool was found to be positive for blood as was the gastric aspirate. She was unable to give a detailed history but denied previous gastrointestinal disease, ulcer symptoms or vomiting of blood. She reported that she was dizzy on standing and that she felt weak. There was a long history of alcohol intake although the patient stated that on average she drank three beers a day. (Subsequent information obtained from the sister indicated that she not only drank large quantities of beer but also whiskey). She had taken ten grains of aspirin on each of the two days prior to arrival. She had apparently experienced a 40 lb weight loss over the previous 12 months and gave a history of easy satiety after eating. Dietary intake was indeterminant.

On initial physical examination blood pressure supine was 140/70 falling to 120/60 in the upright position. The pulse was 140 and was noted to be irregular. Temperature was 100.6°. No other significant physical findings were noted. Electrocardiogram confirmed the presence of atrial fibrillation.

The laboratory examination showed a hemoglobin of 12.6 $g \cdot dl^{-1}$, hematocrit 38%, WBC 4,300 (33 polys, 9 bands, 58 lymphs). Serum chemistries included: sodium 135 $meq \cdot l^{-1}$, potassium 3.7 $meq \cdot l^{-1}$, CO_2 26 $meq \cdot l^{-1}$, calcium 8.8 $mg \cdot dl^{-1}$, glucose 95 $mg \cdot dl^{-1}$, BUN 13 $mg \cdot dl^{-1}$, creatinine 0.7 $mg \cdot dl^{-1}$, bilirubin 1.4 $mg \cdot dl^{-1}$, total protein 6.9 $g \cdot dl^{-1}$ and albumin 3.6 $g \cdot dl^{-1}$. Urinalysis showed 1^+ protein and a few granular casts. The specific gravity was 1.016. Hematest was trace positive. Chest x-ray showed a modestly enlarged heart but no pulmonary congestion.

A gastric tube was placed and dark guaiac material was obtained. The patient was started on intravenous saline solutions and ice water lavage was undertaken. She was seen by surgical and gastrointestinal consultants, both of whom felt that the most likely diagnosis was alcoholic gastritis or possibly a bleeding peptic ulcer. Endoscopy was advised only if the bleeding could not be stopped. The patient was digitalized for the atrial fibrillation. Blood, urine and stool cultures were obtained because of the slightly elevated temperature. The day following admission, the patient was noted to have a large nodular goiter with the left lobe greater than the right. She was also found to have onycholysis and it was suggested that the patient had thyrotoxicosis of the apathetic type. She appeared to be in no difficulty from

the thyrotoxicosis. Because bleeding continued the patient was transferred to the medical intensive care unit. In addition to fluids and digoxin, cimetidine was given intravenously at a dose of 300 mg q6h. The temperature rose to 102.4°. In a few hours the stools became clear of blood as did the gastric aspirate. Diarrhea continued, however, with stools occurring approximately hourly.

On day three the patient was transferred back to the ward because gastrointestinal bleeding had apparently stopped. She appeared to be stable and was in no acute distress. On day six the thyroid function studies obtained on admission were returned and showed a T_4 concentration of 19 $\mu g \cdot dl^{-1}$ and a T_3 resin uptake of >75% confirming the diagnosis of thyrotoxicosis. Quinidine had been started on day five because of continued atrial fibrillation and on day seven the patient was noted to have a regular rhythm for the first time. Diarrhea continued and became essentially yellowish liquid. On day 8 the patient took a marked turn for the worse. Atrial fibrillation returned and urine output decreased to 500 ml in 24 hours with a rise in the serum creatinine to 4 $mg \cdot dl^{-1}$. She became tachypneic and developed rales in the lungs together with edema. Chest x-ray showed pulmonary congestion. The urine was benzidine negative. The patient was started on propylthiouracil 600 mg q4h and an hour after the first dose was placed on 1 g of sodium iodide by intravenous drip. 3 mg of dexamethasone was given q8h and oral propranolol was started at a dose of 20 mg q6h. Thiamine and other B vitamins were also given. On day 9 stools increased to every 30 minutes. Plasma glucose was persistently above 200 $mg \cdot dl^{-1}$. Serum bilirubin rose to 4.3 $mg \cdot dl^{-1}$ with an SGOT of 182 and an alkaline phosphatase of 18.7 KA units. The patient was disoriented and agitated. Urine output became normal after 24 hours of oliguria. On day 10 repeat stool cultures were obtained and the patient was started on cholestyramine because the diarrhea had failed to respond to codeine and Lomotil. She was noted to have a raw, denuded area in the perianal region secondary to the frequent diarrhea. On day 11 the patient appeared critically ill and near death. Cheyne-Stokes respiration was present. A spinal tap showed no significant abnormalities. White blood cell count was 24,000 with a marked left shift. Because of the possibility of staph septicemia secondary to the perianal lesions she was started on methicillin and gentamyacin in large amounts. The diarrhea began to slow and on day 12 she passed no stool. Because of the possibility that cholestyramine might be interfering with the absorption of propylthiouracil the resin was discontinued. Her mental state was slightly improved but she continued to appear critically ill. Diarrhea returned on discontinuation of cholestyramine with 12 bowel movements recorded on day 13. The same day the original TSH determination was reported as undetectable. Repeat T_4 was now 16 $\mu g \cdot dl^{-1}$. On day 14 she was noted to have a 2% drop in the hematocrit and a small amount of blood was found in the gastric aspirate. She was treated conservatively and no major bleeding ensued. Antibiotics were stopped after all cultures were returned as negative. On day 15 the patient appeared to have turned the corner and was able to answer questions for the first time, although intermittent confusion continued. Paregoric was given for the diarrhea and stool frequency held at about four per day. On day 17 the nasal gastric tube was pulled and

the patient was started on liquid feeding. She appeared happy but continued intermittently confused. By day 20 she was eating a regular diet and complaining of continual hunger despite a food intake of about 5,000 calories a day. No hyperglycemia was noted. She was now having formed stools and appeared much improved. On day 23 the T_4 was 12.8 $\mu g \cdot dl^{-1}$. Paregoric was stopped on 2/25/78 and a slight increase in the diarrhea was noted. Her weight had increased from 46 to 51 kilograms and she felt much stronger. She was discharged on propylthiouracil 400 mg q6h, propranolol 20 mg q6h, phenobarbital 15 mg q6h, cymetidine 300 mg q6h and digoxin 0.125 mg daily. She was also given Amphojel and multi-vitamins.

Several weeks after discharge the patient developed a rash thought to be due to propylthiouracil. A similar rash was noted on methimazole. She developed fever - probably a viral illness - and was readmitted. Definitive therapy with radioactive iodine was carried out.

COMMENTS AND SELECTED BIBLIOGRAPHY

1. Clinical picture

Thyrotoxicosis may exist as an almost asymptomatic state or may cause death. The extreme form of the disease is generally categorized as thyroid storm or thyroid crisis and constitutes a medical emergency. It is not possible to provide universally applicable standards for diagnosis but the key issue is fever. Uncomplicated thyrotoxicosis does not cause temperature elevation and the presence of fever greater than 101° should be considered a serious warning of the possibility of storm. Since infection may precipitate thyroid crisis, aggressive treatment of thyrotoxicosis is warranted even if a specific infection has been identified as the cause of the temperature elevation. As outlined in Table I, the full blown picture of storm involves exaggerated hyperthyroidism with fever, cardiovascular signs, altered CNS function and gastrointestinal abnormalities (1-3).

TABLE I

Cardinal manifestations of thyroid crisis

1. Fever (>101°)
2. Cardiovascular signs (tachycardia, arrhythmia, failure)
3. CNS dysfunction (hyperkinesis, psychosis, coma)
4. GI abnormalities (pain, diarrhea)

The physical findings in two large series are shown in Table II.

TABLE II

Presenting signs in thyroid crisis

Finding	Waldstein, et al (1) (n=21)	Mazzaferri and Skillman (2) (n=22)
	%	
Temperature		
< 103	43	41
> 103	57	59
Cardiovascular		
Tachycardia	100	100
Congestive failure	48	50
Arrhythmia	24	36
Shock	0	9
CNS		
Hyperkinesis	43	55
Confusion or somnolence	43	45
Coma	19	18
Psychosis	29	9
Gastrointestinal		
Diarrhea	38	50
Pain	-	14
Jaundice	24	9
Thyromegaly	95	100
Eye signs	55	73

It is interesting that storm developed in the present case against a background of apathetic hyperthyroidism. There was no hyperkinesis, heat intolerance or exophthalmos. The primary clinical manifestations were weight loss, diarrhea and atrial fibrillation. No mention is made in the literature of GI bleeding with thyroid storm. It is likely that the bleeding was due to alcoholism and that it was the precipitating event for storm.

All patients with thyroid storm have abnormal thyroid function tests, but no critical level which always yields the clinical picture of storm can be identified. Overlap between ordinary hyperthyroidism and storm patients is great and neither T_3 or T_4 concentrations will differentiate

the latter from the former (see below). The diagnosis is thus a clinical one in a patient who is proven by laboratory tests to be thyrotoxic. (4) Other laboratory abnormalities have been described as follows.

Hyperglycemia is a frequent accompaniment of thyroid storm and is presumably due primarily to a thyroxine induced block in insulin release (5,6) although it has also recently been noted that thyroid hormone increases the number of glucagon receptors in some tissues (7). The hyperglycemia disappears with reversal of the storm as illustrated in the protocol case.

Anemia is present in a significant number of patients with thyroid storm in contrast to uncomplicated thyrotoxicosis. The mechanism is not clear, although a number of patients with thyrotoxicosis have been reported to have folate deficiency, macrocytosis and decreased red cell survival (8). Leukocytosis in the absence of infection is common in thyroid storm and may reach the leukemoid range (>50,000). Reversible azotemia, presumably pre-renal, is present in up to 25% of patients. Both abnormalities were present in the current case. Liver function studies are abnormal in a significant proportion of patients. Elevated bilirubin and alkaline phosphatase may occasionally suggest obstructive jaundice. Hypercalcemia is rare in thyroid storm and was present in only two of the 43 episodes cited in references 1 and 2.

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2. The mechanism of action of thyroid hormone

The mechanism of action of thyroid hormone is not precisely understood despite intensive study. Permissive amounts of thyroid hormone

are clearly needed for body growth and development of the central nervous system. Inadequate thyroxine neonatally leads to cretinism or stunted growth. Thyroid hormone is likewise permissively involved in hematopoiesis and probably all cellular renewal processes. Apart from its role in growth, major emphasis has been placed on thyroid-induced changes in oxygen consumption and thermogenesis. It has long been known that hypothyroidism can lead to hypothermia and that in thyroid storm body temperatures are high. Even in the absence of fever, thyrotoxicosis or exogenous thyroid increases basal oxygen uptake implying increased heat production. Several factors must be considered in putting together a theory of thyroid hormone action.

a. Energy metabolism: Under normal circumstances the free energy released during oxidation of carbohydrate, lipid or protein is tightly coupled to the production of adenosine triphosphate (ATP) which can then be used for numerous energy requiring reactions in the body (endergonic processes). The bulk of the ATP is generated intramitochondrially in the electron transport chain via oxidation of NADH or succinate as shown in Fig 1.

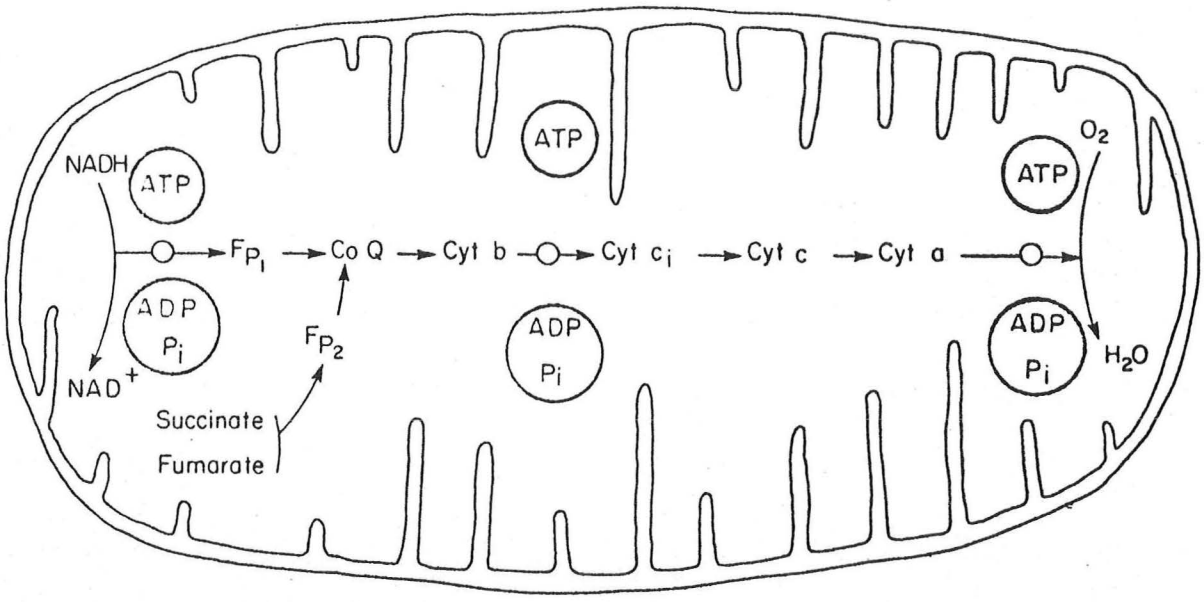

Figure 1. Mitochondrial Oxidative Phosphorylation.

Reduced nicotinamide adenine dinucleotide (NADH) and succinate are products of glucose metabolism. Oxidation of these intermediates is coupled to ATP synthesis from ADP and P_i at the indicated steps. The electron transport system consisting of the flavo proteins (F_p), coenzyme (CoQ) and the cytochromes (Cyt) links the oxidation of the intermediates to reduction of O_2.

The rate of electron flux through the chain (and the simultaneous requirement for oxygen) is primarily determined by concentrations of ATP, ADP and P_i. If ATP stores are high, ADP and P_i will be low and electron transport and oxygen uptake are slow. If ATP concentrations fall, there is a rise in phosphate acceptor (ADP) and electron flow and oxygen uptake is stimulated. Chemicals such as 2,4-dinitrophenol have the capacity to "uncouple" oxidative phosphorylation. As ATP production is reduced electron transport and oxygen uptake become maximal. It was early suggested that thyroid hormone functioned as an uncoupler. For a variety of reasons this theory has been largely abandoned (9). More recently Edelman and his colleagues have suggested that the primary thermogenic action of thyroid hormone is not to reduce ATP synthesis but to increase ATP breakdown. They believe that the primary functional ATPase is the specific Na^+,-K^+-ATPase of the plasma membrane. This enzyme, which is sensitive to inhibition by the cardiac glycoside ouabain, is responsible for the exclusion of sodium from the cell via an exchange reaction with potassium - the sodium pump (Fig 2).

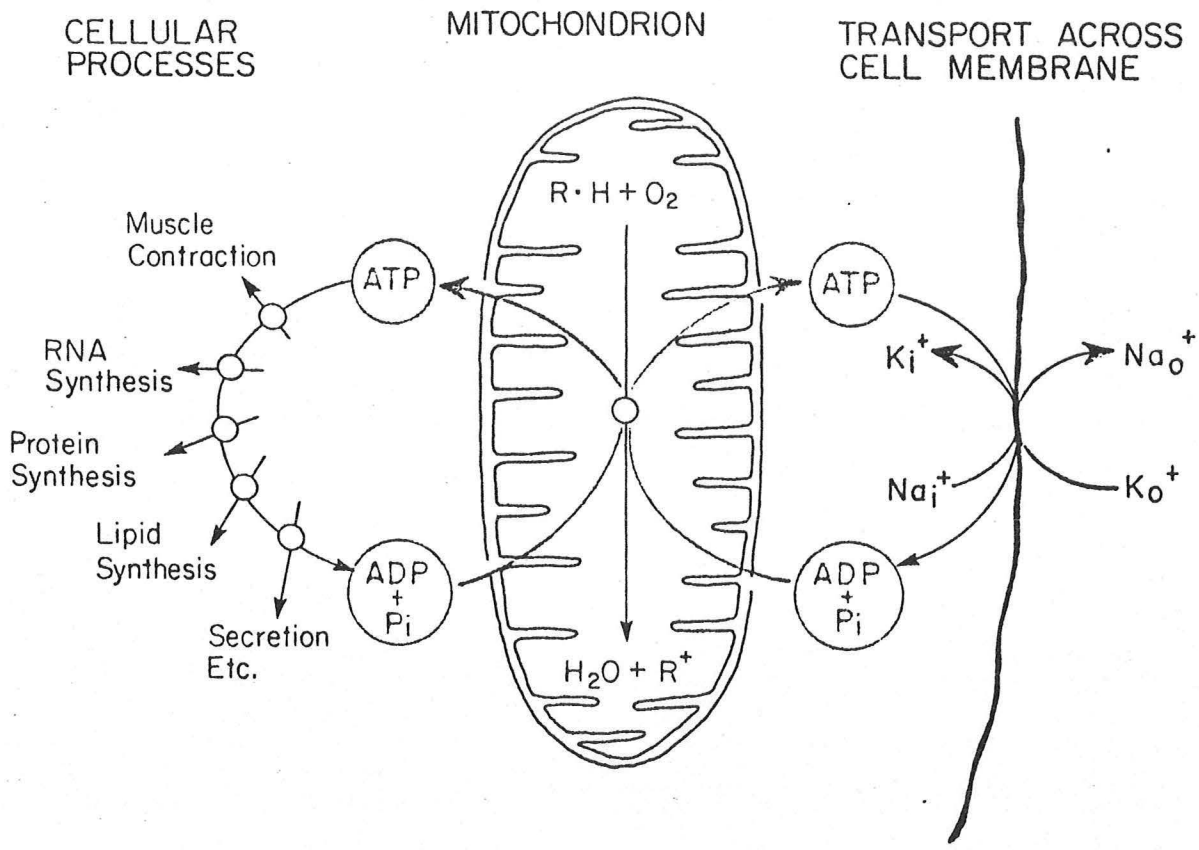

Figure 2. Energy Cycle for Oxidative Metabolism.

ATP generated by mitochondrial oxidative phosphorylation is hydrolyzed to ADP + P_i to provide the energy for a variety of cellular processes — e.g., muscle contraction, macromolecular synthesis, etc. — and for active Na^+ transport (or linked Na^+:K^+ transport) across cell membranes. In the coupled state with NADH, succinate and oxygen in abundance, Q_{O_2} will be paced by rate of formation of ADP + P, as a result of ATP hydrolysis. Na_o = extracellular, and Na_i intracellular Na.

In thyroid responsive tissues it has been found that 40-100% of the increased oxygen uptake induced by thyroid hormone is inhibitable by ouabain. Moreover recent studies have shown that thyroid hormone increases the synthesis of Na^+, K^+-ATPase without altering its rate of degradation (10,11). While the precise mechanism by which increased cycling of the enzyme occurs has not been worked out, it seems likely that a major effect of thyroid hormone is to increase heat production (energy waste) and oxygen uptake via activity of this ATPase. The increased weight loss, negative nitrogen balance and increased food intake of thyrotoxicosis can be considered the consequence of increased substrate need produced by the energy (ATP) drain. It should be noted that thyroxine effects on Na^+, K^+-ATPase cannot account for total action of the hormone. White adipose tissue of the rat is sensitive to thyroxine but the increased oxygen uptake is not ouabain sensitive. Moreover ouabain sensitivity may be substrate dependent (occurring with glucose but not succinate), indicating that one should be cautious in attributing an exclusive role for the Na^+, K^+-ATPase in mediating thyroid action (12).

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b. Mitochondrial enzyme content: Thyroid hormone increases the activity of a number of respiratory enzymes and specifically enhances the content of intramitochondrial (but not cytoplasmic) α-glycerophosphate dehydrogenase as is shown in Table III (13).

TABLE III

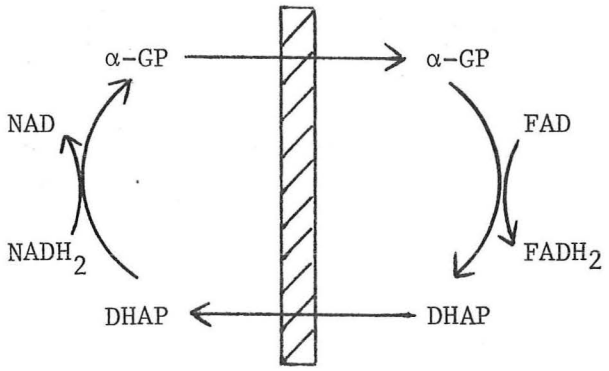
Intramitochondrial α-glycerophosphate dehydrogenase *

State	Liver	Kidney	Adipose
	ΔO.D.·min^{-1}.mg prot^{-1}		
Control	.05	.10	.07
Thyrotoxicosis	1.10	.56	.47

* Adapted from Lee and Hardy, ref cited. No increases were seen in thyroid non-responsive tissues.

The increase in this enzyme parallels the increase in oxygen uptake induced by throxine and occurs only in tissues known to be responsive to thyroid hormone. The importance of the enzyme resides in the fact that it participates in the so-called α-glycerophosphate "shuttle" for transfer of reducing equivalents from cytosol into the mitochondria. The mitochondrial membrane is impermeable to NADH and as a consequence hydride ions must be transported in via permeable substrates. The α-glycerophosphate shuttle is shown in reaction (1).

(1)



Dihydroxyacetone phosphate is reduced to α-glycerophosphate (sn-glycerol-3-phosphate) in the cytosol of the cell with oxidation of NADH. The α-glycerophosphate then crosses the mitochondrial membrane and is reoxidized to dihydroxyacetone phosphate by the intramitochondrial α-glycerophosphate dehydrogenase. Intramitochondrially the electron acceptor is a flavoprotein and FADH rather than NADH is produced. Reference to Fig 1 indicates an important difference in the oxidation of NADH and FADH in the electron transport chain. The oxidation of 1 mole of NADH is coupled to the production of 3 moles of ATP while FADH bypasses the first ATP conservation site. Thus the oxidation of a mole of FADH yields only 2 moles of ATP; i.e., it is energetically less efficient and reducing equivalents entering via this pathway lose more energy as heat (33%) than those entering by shuttles which produce NADH inside the mitochondria (malate-oxaloacetate; β-hydroxybutyrate-acetoacetate). It is of interest that fat cells of obese humans have been reported to be deficient in the intramitochondrial α-glycerophosphate dehydrogenase, a defect which can be repaired by administration of thyroid hormone (14). This suggests that obese subjects do not have the option of utilizing the energetically more wasteful pathway. Presumably a normal person, eating more calories than required to maintain weight, can partially

compensate by shunting more reducing equivalents through the α-glycerophosphate shuttle with the result that at least a third of the extra calories are lost as heat. During fasting or serious illness, T_3 production falls (see below). Since synthesis of mitochondrial α-glycerophosphate dehydrogenase is T_3 dependent, a fall in tissue triiodothyronine should result in diminution of the maximal capacity for α-GP shuttle activity and assure efficient ATP coupling by forcing entry of reducing equivalents through an NADH-generating intramitochondrial reaction. Additional support for a direct mitochondrial effect of thyroid hormone comes from the work of Sterling who has reconfirmed the capacity of T_3 to bind to mitochondrial receptors (15).

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c. Thyroid hormone and catecholamines: Physiologists have long recognized that thyroid hormone was important in the regulation of catecholamine effects on metabolism and the circulation. Moreover, many of the symptoms of thyrotoxicosis are known to resemble hyperactivity of the sympathetic nervous system. The classic study of Brewster, et al (16) showed that the physiologic changes produced by thyroid feeding (to induce thyrotoxicosis) could be reversed by total sympathetic block. The same changes were reproduced by the infusion of epinephrine or norepinephrine in the face of the sympathetic block. Quantitatively, the response to catecholamines was related to the plasma level of thyroid hormone. Recent studies have shown that thyroid hormones increase the number of β-adrenergic receptors in the heart (17,18) without a change in affinity for the hormone (Table IV). Such a change could account for an increased response to catecholamines in the absence of increased circulating concentrations of hormone. It has also been claimed that β_2 agonists directly stimulate thyroxine release from the thyroid gland (19) while alpha agonists block the response to TSH (20). There has been some suggestion that alpha and beta receptors can be interconverted by thyroid hormone or its lack.

TABLE IV

Effect of thyroid hormone on number and affinity of rat cardiac β-adrenergic receptors

Treatment	Binding sites (fmol·mg prot^{-1})	Kd (affinity) (nM)
None	89 ± 5	12 ± 5
T_3	196 ± 7	15 ± 8
None	100 ± 6	16 ± 4
T_4	180 ± 20	19 ± 6

Data taken from ref 17. Animals were treated for three days with T_3 or T_4 and cardiac membranes were isolated. Binding was assayed with (-)-[^{3}H] dihydroalprenolol.

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d. Thyroid hormones, nuclear binding and protein synthesis: It is now known that thyroid hormone exists in three major forms in tissue and plasma (other derivatives are also known). These are thyroxine (3, 5, 3', 5'-tetraiodothyronine), triiodothyroxine (3, 5, 3'-triiodothyronine) and reverse T_3 (3, 3', 5'-triiodothyronine). Thyroxine (T_4) is secreted exclusively from the thyroid gland and is converted via deiodination to one or the other of the two T_3 compounds (21-23). Reverse T_3 is thought to be metabolically inactive while the consensus holds that T_3 is the physiologically active form of thyroid hormone.

Figure 3

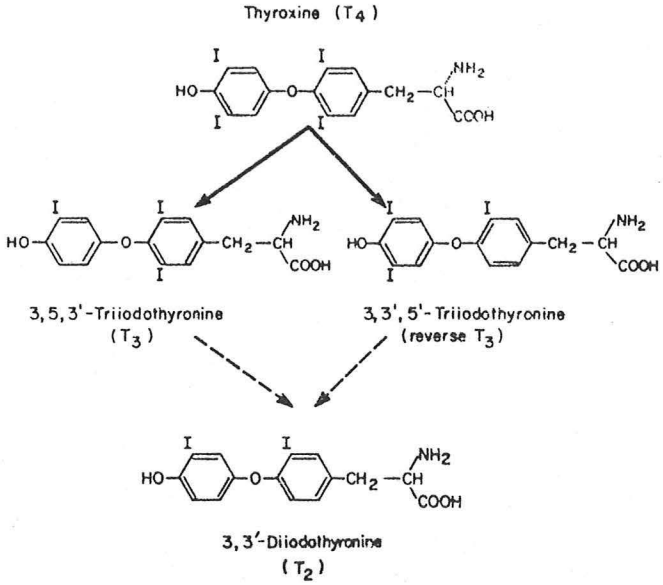


Figure 3 Structural formulas of thyroxine and several of the products of thyroxine deiodination.

About 20% of the T_3 produced daily comes directly from the thyroid while 80% is derived from peripheral deiodination of T_4. 97 or 98% of reverse T_3 is produced by peripheral conversion (22). In a variety of acute and chronic illnesses, particularly those accompanied by semi-starvation and weight loss, there is a fall in T_3 concentration and a rise in rT_3 levels. Teleologically one supposes that rT_3 production represents an inactivating pathway for thyroid hormone designed to conserve energy by diminishing caloric loss as heat. Interestingly, rT_3 levels are increased by the hyperthyroid state (24). Serum values in normals are shown in Table V.

TABLE V

TABLE 5 Serum rT_3, T_4 and T_3 concentrations (mean ± SD) in normal subjects and patients with various thyroid diseases

	N	Serum rT_3 ng/dl	Serum T_4 μg/dl	rT_3/T_4 ng/μg	Serum T_3 ng/dl
Normal	106	23 ± 8	8.2 ± 1.7	2.8 ± 1.1	104 ± 26
Hyperthyroidism	22	90 ± 49	21.6 ± 4.7	4.2 ± 2.2	446 ± 172
T_3-hyperthyroidism	5	36 ± 13	9.5 ± 2.6	3.8 ± 0.9	232 ± 75
Hypothyroidism	21	14 ± 5	2.6 ± 1.2	6.7 ± 4.0	72 ± 34
Pregnancy	39	49 ± 9	11.5 ± 3.8	4.5 ± 1.5	150 ± 49
Cord serum	7	280 ± 143	7.9 ± 2.2	3.5 ± 1.6	45 ± 18

Considerable evidence has now been obtained to indicate that T_3 is preferentially bound to receptors localized on nuclear chromatin. The nuclear receptors are highly specific and binding affinity for analogues of thyroid hormone appears to directly parallel biological activity (25). Moreover, nuclei from tissues such as testis and spleen - generally thought to be thyroid unresponsive - had few receptors when compared to nuclei from liver, kidney, heart and pituitary, tissues that are known to be thyroid responsive. The nuclear binding sites, which are non-histone proteins, have been partially purified from rat liver (26). It can be shown that over 85% of receptor-found iodothyronine is T_3 and only about 15% T_4 (27). While biological activity of T_4 cannot be absolutely ruled out, the preferential binding of T_3 suggests its primacy.

TABLE VI

Hepatic Nuclear T_3 and T_4 Concentrations Measured by Radioimmunoassay

	Extraction of nuclei*	Recovery*‡	Nuclear T_3 and T_4		
			DNA	DNA	Total pmol
	%		*ng/mg*	*pmol/mg*	%
T_3	89.8±3.5	41.6±7.5	0.33±0.12	0.51±0.19	86.8±9.0
T_4	93.1±1.0	36.1±5.9	0.06±0.04	0.08±0.06	13.2±9.4

Each entry is the mean±SD for 13 euthyroid rats. The mass of injected ^{131}I-T_3 recovered in the nuclei was subtracted from the individual T_3 measurements. The mass of ^{131}I-T_3 was calculated as the product: T_3 recovery × mean nuclear T_3 concentration of three athyreotic rats, 0.06±0.01 ng/mg DNA. As assessed from the injected ^{131}I-T_3 dose and kinetic parameters (see Table III), the nuclear T_3 measured in the athyreotic rats was fully attributable to the nonradioactive T_3 in the injected ^{131}I-T_3 dose. Nuclear T_4 was not detectable in the athyreotic rats.

* Calculated from the cpm of ^{131}I-T_3 and ^{125}I-T_4 in the nuclei before extraction and the separate counting rates in the ethanolic extract.

‡ Determined before radioimmunoassay.

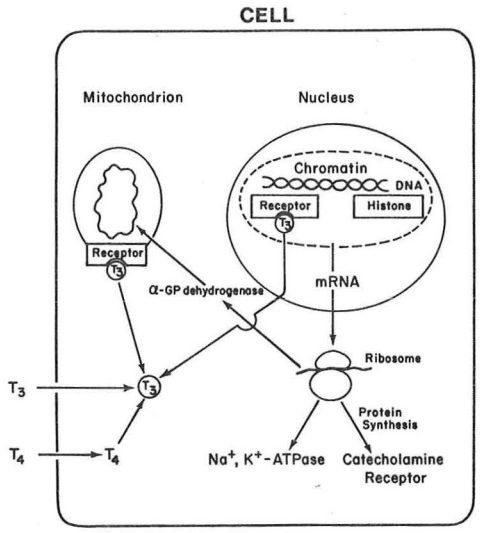
The T_3-receptor complex (but not free T_3 or T_3 bound to plasma carrier protein) can bind to DNA and induce the formation of poly (A) containing messenger DNA which codes for specific thyroid related proteins (26,28).

A speculative overview of thyroid hormone action consistent with known facts is shown in Fig 4. According to this formulation T_4 is deiodinated to T_3 in the cytosol of the cell. The T_3 is then bound to specific receptors in the nucleus and the receptor-T_3 complex then activates translation of specific messenger RNA(s) which code for new protein synthesis. Some of the proteins induced might include the Na^+, K^+-ATPase, the mitochondrial α-glycerophosphate dehydrogenase and the β-receptor for catecholamines. In view of the reported mito-

chondrial binding of T_3, the possibility has to be kept open that mitochondrial protein synthesis is stimulated directly. No cytosolic receptor for T_3 is shown in this scheme.

Figure 4

MECHANISM OF ACTION OF THYROID HORMONE



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3. The initiation of thyroid storm

The mechanisms by which thyrotoxicosis is converted to thyroid storm are unknown. It is clear that mean levels of circulating T_4 and T_3 are not different in the two forms of the disease (4,29). What is not known is whether in a given patient a brisk rise in hormone release (still within the mean normal hyperthyroid range) might herald the onset of storm. The patient of Jacobs, et al (30), who had T_3 levels drawn prior to the onset of surgery-induced crisis, showed a modest increase in T_3 concentrations after storm had developed. The rare syndrome of I^{131}-induced storm (31) presumably results from increased release of thyroid hormone. On the other hand most authors feel that thyroid crisis is linked to an altered peripheral response to an already elevated thyroid hormone concentration. Nicoloff and Dowling (32) have shown that liver uptake of T_4 is increased in thyrotoxicosis and suggest that there is enhanced deiodination under such circumstances. It is conceivable that accelerated conversion of T_4 to T_3 in target tissues is the primary event of thyroid storm. This increased conversion would not necessarily be reflected in plasma T_3 levels.

TABLE VII

Plasma concentration and production rates of

epinephrine and norepinephrine in thyrotoxicosis*

	Control	Hyperthyroidism	Hypothyroidism
1. Epinephrine			
Concentration ($ng \cdot dl^{-1}$)	3 ± 3	4.4 ± 3.5	4.7 ± 3.5
Production ($ng \cdot kg^{-1} \cdot day^{-1}$)	40 ± 11	51 ± 27	43 ± 20
2. Norepinephrine			
Concentration ($ng \cdot dl^{-1}$)	15.7 ± 3	18.7 ± 2.8	33.7 ± 4.8
Production ($ng \cdot kg^{-1}$)	146 ± 35	174 ± 49	462 ± 9.98

* Data from refs 33, 34

It has long been known that most episodes of thyroid crisis are precipitated by infection, surgery or some other form of stress. In view of the synergistic relationship between thyroid hormone and catecholamines mentioned previously the possibility has to be considered that increased adrenergic activity somehow induces the clinical syndrome. Plasma levels and secretion rates of both epinephrine and norepinephrine are normal in thyrotoxicosis (33,34), but, again, sequential values in a given patient before and after storm are not available. (Table VII)

At present, therefore, it is impossible to identify the specific mechanisms by which storm is induced. Intuitively I favor (slightly) a catecholamine mechanism, partly because maximum effects of a single dose of thyroxine may require 48 hours to develop while storm can be precipitated much earlier.

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4. Treatment

Thyroid storm represents a medical emergency with high mortality rates (20-50%). All patients should be treated with antithyroid drugs in large amounts. Recent studies have shown that propylthiouracil slows the peripheral conversion of T_4 to T_3 while methimazole has much less (if any) capacity to inhibit 5' deiodination (35-38). For this reason propylthiouracil should always be used and an initial dose of 1000-1200 mg should be given. Organification of iodide in the thyroid gland is inhibited by one hour under these circumstances. If the patient is unconscious the medication will have to be ground up and administered via nasogastric tube. Propylthiouracil should be continued in high doses (200-400 mg q6h) until symptoms are controlled following which the dosage is gradually tapered.

While propylthiouracil rapidly blocks thyroid hormone synthesis,

it does not prevent continued release of pre-formed thyroxine. For this reason iodides are given approximately one hour after the propylthiouracil. The usual practice is to give 1 g of sodium iodide IV every 12 hours the first day followed by 30 gtts of a saturated solution of potassium iodide daily for the next week to 10 days.

Steroids have been routinely administered for many years. The original assumption was that hyperthyroidism caused increased metabolism of hydrocortisone resulting in a state of relative adrenal insufficiency. Recent studies of Gordon and Southren (39) confirm the increased production rate of cortisol and aldosterone but do not indicate adrenal insufficiency in uncomplicated hyperthyroidism (Table VIII).

TABLE VIII

Cortisol metabolism in thyroid disease*

Test	Control	Hyperthyroid	Hypothyroid
Secretion rate ($mg \cdot day^{-1}$)	20	70	8
Miscible pool (mg)	1.7	1.3	1.6
$T_{\frac{1}{2}}$ (min)	84	25	172
Plasma level ($\mu g \cdot dl^{-1}$)	14	10	17
Urinary 17OH ($mg \cdot day^{-1}$)	8	17	3

* Data from ref 39

It is now recognized that glucocorticords (at least dexamethasone) block the conversion of T_4 to T_3 and increase the production of rT_3 (40). It is likely, therefore, that the large doses of hydrocortisone given previously in thyroid crisis acted peripherally to block T_3 production rather than to abort a relative adrenal crisis. The use of steroids should be considered routine in thyroid storm. 2 mg of dexamethasone should be given parenterally every six hours until the crisis has been reversed and gradually tapered thereafter. The change in serum concentrations of thyroid hormones in hyperthyroid patients using propylthiouracil ($150\ mg \cdot 6h^{-1}$), SSKI ($3\ gtts \cdot 6h^{-1}$) and dexamethasone ($2\ mg \cdot 6h^{-1}$) is shown in Table IX (41). While T_4 values remained elevated, T_3 concentrations were normal within 24 hours. The fall in T_3 with combined therapy was considerably faster than with propylthiouracil alone and also faster than with propyl plus iodides.

TABLE IX

Thyroid hormone values after combined treatment with propylthiouracil, SSKI and dexamethasone *

Hormone	Days			
	0	1	2	3
T_4 ($\mu g \cdot dl^{-1}$)	20.3	21.1	21.0	19.3
T_3 ($ng \cdot dl^{-1}$)	468	160	138	121
rT_3 ($ng \cdot dl^{-1}$)	84.5	342	242	190

* Data from ref 41

In addition to these specific measures supportive treatment will require 2-3 liters of fluids (because of the large insensible water loss), thiamine and other B vitamins, oxygen and sedation (probably with phenobarbital). There is some question as to the effectiveness of digitalis in thyroid heart failure, but it probably should be given with a dilating heart and pulmonary congestion. It will also be required for atrial fibrillation if present. Cooling measures are rarely required unless temperature reaches 105° or greater.

An overall schedule of therapy (which may have to be modified in the individual patient) is as follows:

Specific therapy

1. Propylthiouracil as a one gram bolus immediately followed by 200-400 mg q6h.
2. Dexamethasone 2 mg parenterally immediately and q6h.
3. Sodium iodide 1 g intravenously 1 hour after propylthiouracil; repeat q12h.

Supportive therapy

1. IV fluids
2. Thiamine and other B vitamins
3. Oxygen
4. Sedation with phenobarbital
5. Digitalis
6. Cooling

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a. Propranolol: While there is widespread agreement about the general plan of treatment of thyroid storm (42-45) the question of the use of propranolol remains controversial. Since the report of Das and Krieger (46) the β-blocker has been extensively used, occasionally in the absence of other therapy (47). There seems to be little question that many of the symptoms of thyroid crisis can be ameliorated by propranolol. Recent evidence indicates that in addition to its other effects the drug blocks the conversion of T_4 to T_3 and increases the concentration of rT_3 in similar fashion to propylthiouracil and dexamethasone (48,49). The concern with propranolol has to do with its depressant effects on the myocardium. Pietras, et al (50) and Ikram (51) have emphasized that an elevation of left ventricular end diastolic pressure and heart failure are common in thyrotoxicosis and that in these circumstances propranolol might cause difficulty. While 2 mg of intravenous propranolol caused a 13% fall in cardiac output in uncomplicated thyrotoxicosis the drop was 30% when heart failure was present in Ikram's study (51). Pietras, et al showed a 30% decrease in the mean cardiac index of 7 thyrotoxic patients after beta blockade. Since cardiac dilatation is an extremely common feature of full blown thyroid storm, propranolol should be used with caution in my opinion. In the case of allergy to antithyroid drugs or failure to respond to routine therapy in a patient with life-threatening crisis, propranolol may be indicated.

If given IV, the maximum dose should probably be 5 mg (47). With oral dosage larger than usual amounts may be required in thyrotoxic patients. A high degree of peripheral blockade requires plasma levels of 50-100 $mg \cdot dl^{-1}$ (52). Hellman, et al (53) reported that 8 of 11 thyro-

toxic subjects did not achieve this level when given 40 mg of propranolol orally every six hours. The latter authors attributed the failure of Eriksson et al (54) to prevent thyroid storm with propranolol to this phenomenon.

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b. Extracorporeal treatment: There has been modest interest in the lowering of plasma thyroid hormone levels by extracorporeal methods. This has been done with blood exchange and plasmapheresis (55) and by dialysis techniques against resins or charcoal (e.g., 56). Such treatment will never be part of the routine therapy of thyroid storm and should only be entertained as a last ditch measure in a dying patient.

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c. The problem of diarrhea: The protocol case exhibited profound diarrhea, and this diarrhea was unresponsive to symptomatic treatment. She appeared to respond to cholestyramine therapy with cessation of diarrhea when the resin was given. Diarrhea returned when cholestyramine was discontinued. The cause of diarrhea in thyrotoxicosis is unknown. Major emphasis has been placed on hypermotility of the intestinal tract (57). Some patients have frank steatorrhea (57,58). The present patient started with mushy, melanotic stools and moved to a stool which was essentially pure water. It is known that bile acids have the capacity to stimulate colonic secretion of fluid, presumably by inducing cyclic AMP formation in the colon (59,60). Presumably cholestyramine would only inhibit diarrhea due to bile acid excess (61). I was unable to find data on bile salt flow in hyperthyroidism in man. In the experimental animal, Layden and Boyer (12) have shown that hyperthyroidism increases bile salt excretion secondary to stimulation of bile salt independent bile flow mediated by canalicular Na^+, K^+-ATPase activity. If the same mechanism is operative in humans, it is possible that at least a portion of the diarrhea is bile salt-induced. This would account for the dramatic effect of cholestyramine in the present patient.

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