THE HEART AND HYPERTHYROIDISM

C. Lynn Skelton, M.D.

Medical Grand Rounds

Parkland Memorial Hospital

Dallas, Texas

December 4, 1975

OUTLINE

INTRODUCTION

CARDIAC PATHOPHYSIOLOGY IN HYPERTHYROIDISM

- Mechanism of Action of Thyroid Hormones
- Sympathoadrenal-Thyroid Interactions
- Direct Cardiac Effects of Thyroid Hormones
- Cardiac Hypertrophy and Failure in Hyperthyroidism

CLINICAL MANIFESTATIONS

- Signs and Symptoms
- Electrocardiographic Findings
- Roentgenographic Findings
- Apathetic Hyperthyroidism

TREATMENT OF THYROID HEART DISEASE

INTRODUCTION

The cardiac manifestations of hyperthyroidism are among the earliest and most consistent phenomena of this disorder. Palpitations, tachycardia, arrhythmias, cardiac enlargement, increased pulse pressure and occasionally even frank congestive heart failure are among the clinical signs referable to hyperthyroidism. Over the years a great deal of controversy has been generated in two specific areas: (1) The basic pathophysiologic mechanism for the hyperdynamic circulatory state and (2) whether or not hyperthyroidism alone can result in cardiac hypertrophy and/or congestive heart failure in the absence of an additional complicating cardiac abnormality. In this presentation we will briefly review the available clinical and experimental evidence concerning the pathophysiology of the cardiac manifestations of hyperthyroidism in an attempt to provide a rational framework for the diagnosis and treatment of this disorder. Emphasis will be placed on recent experimental animal studies due to the relative paucity and impracticality of comparable studies in man.

CARDIAC PATHOPHYSIOLOGY IN HYPERTHYROIDISM

Mechanism of Action of Thyroid Hormones

At this time there is no generally accepted unifying hypothesis which can explain the multifaceted actions of thyroid hormones. However, two hypotheses which have recently been advanced may help clarify a number of aspects of thyroid hormone action at the molecular level. The first bears on the mechanism of initiation of thyroid hormone effects in the cell nucleus, and the second attempts to relate thyroid hormone effects to sodium transport and thermogenesis.

Increasing evidence suggests that thyroid hormones initiate their effects by augmentation of the transcription of genetic information. This concept was introduced by Tata and his co-workers on the basis of observations in thyroidectomized rats injected with triiodothyronine (1). The first biochemical change noted was an increased incorporation of orotic acid into rapidly labeled nuclear RNA. Incorporation was soon followed by stimulation of RNA polymerase, and later by an increase in the rates of protein synthesis and oxygen consumption. Inhibitors of protein synthesis, such as actinomycin D, could block the effects of thyroid hormone (2). These findings suggest that the effects of thyroid hormones are largely caused by new protein synthesis brought about by enhanced transcription of DNA. Although some workers still favor the mitochondria as the initial site of action of thyroid hormone (3,4), the recent demonstration of specific nuclear binding sites for iodothyronines provides further support for Tata's viewpoint (5). The preferential binding of T_3 rather than T_4 also supports the premise that the biologically active thyroid hormone is primarily T_3.

A characteristic effect of thyroid hormone in virtually all sensitive tissues is an enhancement of resting oxygen consumption and heat production. Recent reports from Edelman's laboratory suggest a relationship between the calorigenesis induced by thyroid hormone and the energy required for maintenance of intracellular-extracellular sodium and potassium gradients (6). The maintenance of low intracellular sodium and high intracellular potassium concentrations is a function of the membrane-bound enzyme, Na^+-K^+ ATPase. The ion exchange activity of this sodium pump accounts for over half of the body's total caloric expenditure in the euthyroid state. Edelman found that the in vitro addition of ouabain, considered to be a specific inhibitor of Na^+-K^+ ATPase, substantially reduced the enhancement of oxygen consumption which results from T_4 administration (6). On the basis of this observation it was postulated that a major role of thyroid hormones is stimulation of Na^+-K^+ ATPase activity. As shown schematically in Figure 1, the activation of Na^+-K^+ ATPase results in increased production of ADP from ATP. Since ADP tightly controls mitochondrial oxygen consumption, the net effect is increased oxygen consumption and ATP generation providing a possible explanation for the calorigenic effects of thyroid hormones. It has been postulated that this activation of Na^+-K^+ ATPase results from the synthesis of proteins one or more of which affects energy consumption in active Na^+ transport, thus, conforming to the basic mode of initiation of thyroid hormone effects suggested by Tata (Figure 2). Although neither of these hypothesis has been confirmed, they do provide a possible basis for understanding the multiplicity of cellular effects produced by thyroid hormones and should be considered in any attempt to explain the effects of thyroid hormones on the heart.

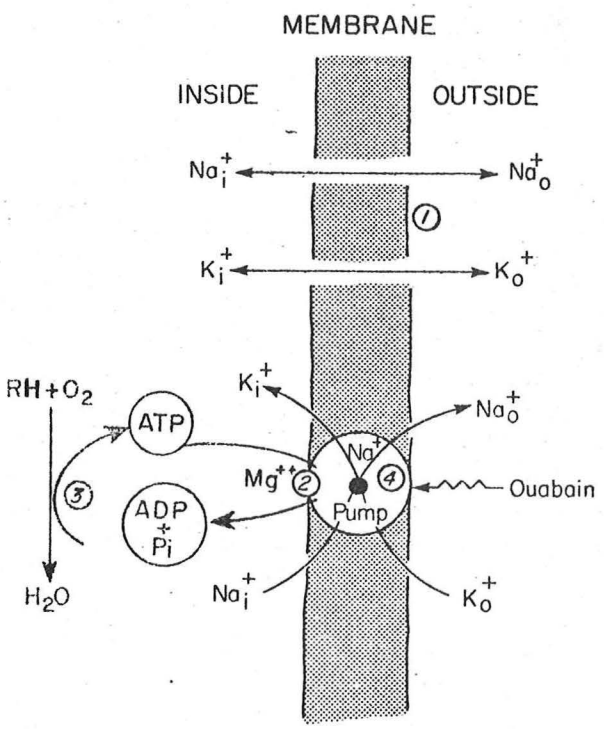

Figure 1

Sites of Regulation of Na^+ transport across Cell Membrane.

Site 1 indicates passive Na^+ and K^+ permeability channels. Site 2 is the coupling of ATP hydrolysis to active Na^+ transport (or Na^+-K^+ linked transport). Site 3 designates the regeneration of ATP coupled to oxidation of reduced substrates (e.g., NADH, succinate). Site 4 indicates actions on the Na^+ pump either by stimulation of a set of pre-existing pumps or by increasing the number of pumps.

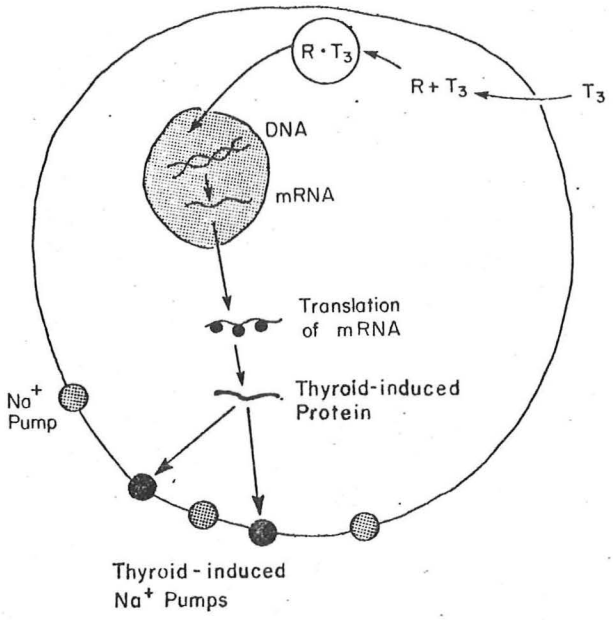

Figure 2

Speculative Model of Thyroidal Control of Na^+ Pump Activity via Induction of RNA and Protein Synthesis.

T_4 is assumed to bind to an intracellular receptor that regulates RNA-dependent DNA synthesis. The induced messenger RNA (mRNA) dictates the synthesis of proteins, one or more of which affect energy consumption in active Na^+ transport. This effect may be a result of the synthesis of new pumps and insertion in membrane loci or the unmasking of dormant pump sites or augmentation of the activity of sites previously present and active.

Sympathoadrenal - Thyroid Interactions

The striking similarities between the effects of excessive thyroid hormone and enhanced sympathoadrenal activity have long been recognized. A definite adrenergic contribution to the clinical manifestations of hyperthyroidism was first suggested by the finding that total or near total sympathetic block produced by the subarachnoid injection of procaine could successfully relieve or prevent thyrotoxic storm (7). With this information in mind, Brewster and co-workers (8) performed a landmark study in dogs which unequivocally demonstrated a major role for the sympathoadrenal system in producing the cardiovascular manifestations of experimental hyperthyroidism. This study stimulated the use of sympatholytic agents such as reserpine (9), guanethidine (10), and more recently, propranolol (11,12), as therapy for hyperthyroidism in man. These agents uniformly decreased the tachycardia, pulse pressure, cardiac output and oxygen consumption toward normal levels in these patients. Thus, it seems clear that a substantial portion of the cardiovascular manifestations of hyperthyroidism are due to sympathoadrenal

activity. However, despite extensive investigation a great deal of uncertainty still persists in regard to the exact nature of the sympathoadrenal-thyroid hormone interaction in the heart.

Possible interactions between thyroid hormones and the sympathoadrenal system include:

1. Adrenergic receptors of target cells might be sensitized by thyroid hormone to the activating effects of catecholamines resulting in a potentiated response.

2. Tissue levels of free catecholamines might be increased by thyroid hormone via one of several mechanisms:

    a. Interference with catecholamine inactivation or removal.

    b. Increased catecholamine release from the adrenals.

    c. Increased catecholamine release per sympathetic nerve impulse.

    d. Increased sympathetic nerve impulse traffic from the central nervous system.

Most of the studies reported prior to 1960 suggested that both the pressor and chronotropic responses to exogenously administered catecholamines were potentiated by hyperthyroidism (13,14). The most influential report in this regard was the previously mentioned study by Brewster and co-workers (8) in euthyroid and hyperthyroid dogs. These investigators studied the effects of catecholamine infusion after thiopental anesthesia and spinal epidural block with procaine. Procaine block was used in an attempt to inhibit the sympathetic nervous system. They found that the increases in heart rate, cardiac index, left ventricular stroke work, and oxygen consumption seen in the hyperthyroid dogs were reduced to euthyroid levels after procaine block. Futhermore, they reported that either epinephrine or norepinephrine infusion caused a greater increase in heart rate, cardiac index, and oxygen consumption in the hyperthyroid animals than in the euthyroid dogs. On the basis of these findings, Brewster suggested that the metabolic and hemodynamic effects of hyperthyroidism were not the result of a direct action of thyroid hormone, but rather were due to the physiologic effects of catecholamines as augmented by excess thyroid hormone. However, careful analysis of Brewster's data reveals several inconsistencies and shortcomings. For instance, both norepinephrine and epinephrine produced greater effects on heart rate, cardiac index, and right ventricular stroke work in hyperthyroid dogs, but only norepinephrine produced an enhanced fall in atrial pressures. The effects of neither amine on blood pressure and left ventricular stroke work

were increased in hyperthyroidism. None of their data was subjected to statistical analysis. Furthermore, spinal epidural blockade with procaine does not specifically block sympathetic nerve impulses; thus, blockade of parasympathetic or spinal reflexes could well have influenced the results. A more critical error was the use of only a single dose of epinephrine or norepinephrine in the studies designed to test for catecholamine hypersensitivity in hyperthyroidism. As succinctly delineated by Trendelenberg (15) any conclusions regarding tissue catecholamine hypersensitivity require studies utilizing a wide range of catecholamine concentrations in order that a decrease in either the threshold concentration or half-maximal activity (K_m) can be shown.

In general, virtually all of the early studies (13,14) purporting to show an altered responsiveness to the cardiovascular effects of catecholamines in hyperthyroidism shared one or more of the defects of the Brewster study (8). Thus, their conclusions must be viewed with considerable skepticism.

More recently, a number of studies have appeared that have largely met the criticisms mentioned above (16-23). Almost invariably, these latter studies have failed to document an enhanced sensitivity of the cardiovascular system in hyperthyroidism to the effects of exogenous or endogenous catecholamines. Van der Schoot and Moran (16) found no potentiation of the positive inotropic or chronotropic effects of epinephrine and norepinephrine on the isolated dog heart (Figure 3) or on the isolated atrium or ventricular strip of thyroxine-treated rats. These workers (17) also performed a study similar in many regards to that of Brewster, et al (8), using epidural block with procaine but were unable to find any evidence of catecholamine hypersensitivity in hyperthyroid dogs. Margolius and Gaffney (18) found similar blood pressure and heart rate responses to exogenously administered norepinephrine and to several frequencies of cardiac sympathetic nerve stimulation in hyperthyroid and euthyroid dogs (Figure 4). Cairoli and Crout (19) noted no alteration in the heart rate response to various concentrations of norepinephrine in hyperthyroid rats. Buccino, et al (20) and Levey, et al (21) noted no enhancement of the contractile effects of graded doses of norepinephrine in isolated papillary muscles from hyperthyroid cats (Figure 5).

Similar studies in man have tended to confirm the recent experimental animal studies. Wilson and his associates (22,23) found that isoproterenol, epinephrine, and norepinephrine produced similar increases in heart rate and decreases in mean atrial and mean arterial pressures in euthyroid human subjects before and after triiodothyronine-induced hyperthyroidism.

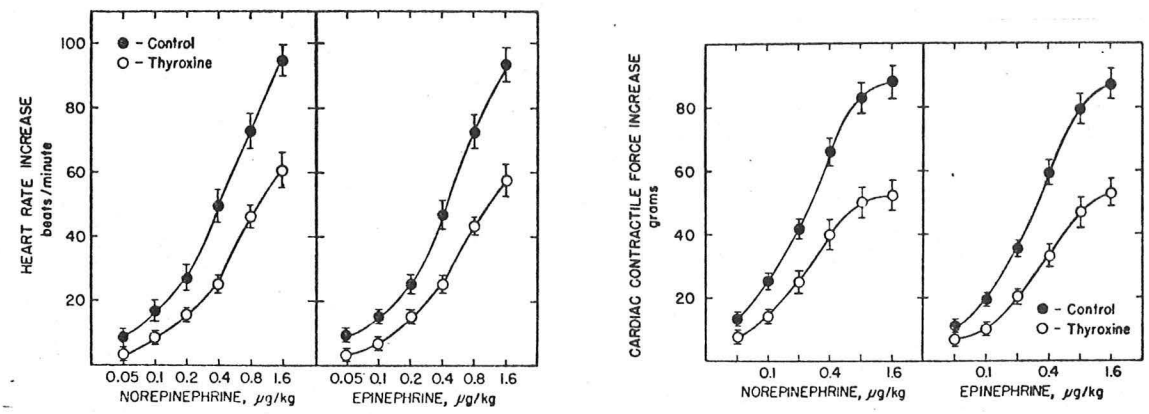

Figure 3
From Van der Schoot and Moran (16)

Influence of graded doses of norepinephrine and epinephrine on heart rate and cardiac contractile force of 17 normal dogs and 17 dogs pretreated with thyroxine (1 mg/kg/day) for 3 weeks.

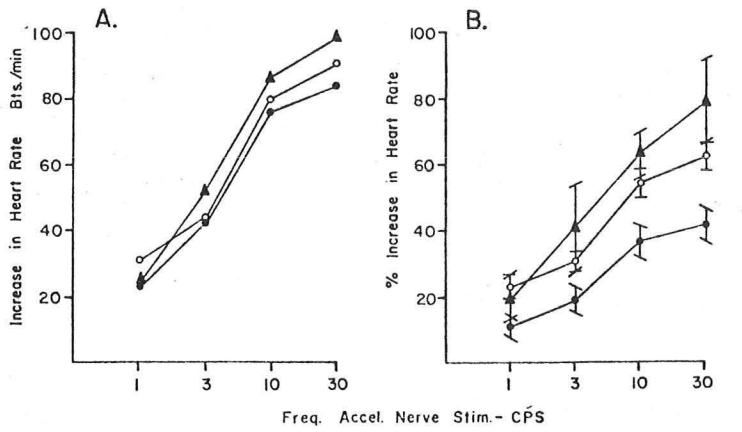

Figure 4
From Margolius and Gaffney (18)

Effects of accelerator nerve stimulation on heart rate in control, thyroid fed, and radio-iodine treated dogs. Control (20 dogs). ○—○ Thyroid fed (11 dogs) ●—● Hypothyroid (6 dogs) ▲—▲

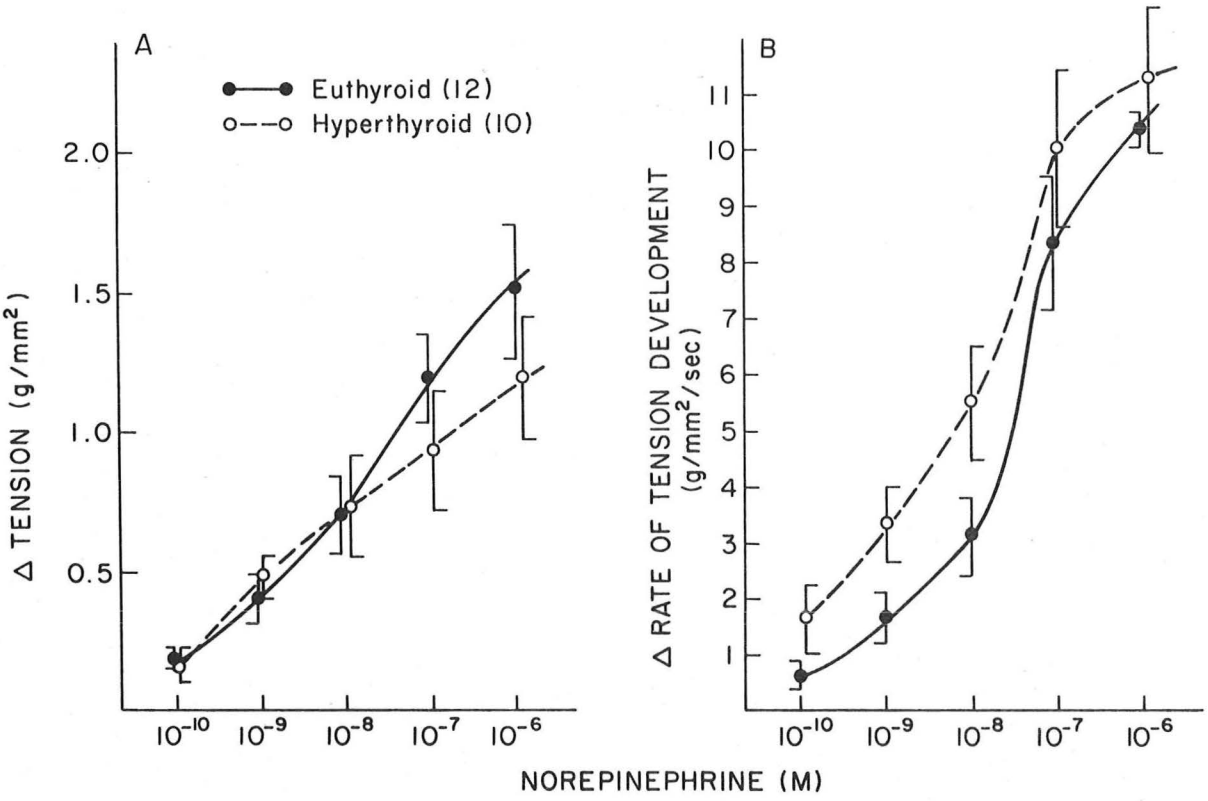

Figure 5
From Levey, et al (21)

Effects of norepinephrine on isometric tension and rate of tension development in isolated right ventricular papillary muscles from 12 euthyroid and 10 hyperthyroid cats.

In contrast to these studies, Wildenthal (24) recently reported that spontaneously-beating hearts from late fetal mice sustained in organ culture had an enhanced sensitivity to the chronotropic and arrhythmogenic effects of exogenously administered norepinephrine. The physiologic significance of these findings in artifically supported fetal hearts whose endogenous catecholamine content has been depleted remains to be determined.

In summary, the weight of experimental evidence at this time strongly suggests that the heart is not hypersensitive to the effects of catecholamines in hyperthyroidism. It therefore seems likely that increased tissue levels of catecholamines must be responsible for the prominent adrenergic component of the hyperdynamic circulatory state of hyperthyroidism. Such an increase in tissue levels is probably not brought about by increased norepinephrine release from cardiac sympathetic nerve terminals since Margolius and Gaffney (18) found no enhancement of the heart rate response when the cardioaccelerator nerves were stimulated in hyperthyroid dogs (Figure 4).

The possibility that increased adrenal medullary secretion of catecholamines could contribute to the cardiovascular manifestations of hyperthyroidism has been the subject of numerous conflicting reports (25). The current consensus is that hyperthyroidism does not significantly alter the plasma or urinary levels of catecholamines or their metabolites. Future contributions in this area using more sensitive and reproducible techniques may help to resolve this question.

Myocardial inactivation of epinephrine has been studied by Wurtman and co-workers (26) in hyperthyroid rats. They found that the activity of the two enzymes which break down catecholamines, catechol-O-methyl transferase and monamine oxidase were not altered by hyperthyroidism. However, they noted that a greater amount of injected ^{3}H-epinephrine or ^{3}H-norepinephrine is delivered to the heart in hyperthyroidism and that there is a concomitant decrease in catecholamine binding or inactivation resulting in an increased myocardial catecholamine level. If such a mechanism were operative it would be expected that the cardiac response to a given dose of catecholamine would be enhanced in hyperthyroidism. Several previously mentioned studies have failed to document such a potentiation both in the rat as well as other species (16-23). Thus, the importance of these findings by Wurtman remains to be defined.

The possibility that enhanced sympathetic nerve traffic resulting from central nervous system activation may account for the adrenergic stimulation characteristic of hyperthyroidism has not been investigated. Such a mechanism would act by increasing the concentration of catecholamine at cardiovascular effector sites rather than altering the sensitivity of these receptors to a given amount of catecholamine. In view of the prominent central nervous system effects frequently seen in hyperthyroidism, this would appear to be a fertile area for future research.

Direct Cardiac Effects of Thyroid Hormones

The possibility that thyroid hormone exerts a direct effect on the heart independent of the sympathoadrenal system was suggested as early as 1932 by Markowitz and Yater (27). These workers studied the effect of thyroxine added to heart fragments of two day old chick embryos which were devoid of functioning adrenergic tissue. They found that the rate of beating of those cells incubated with thyroxine was significantly greater than that of controls after twelve hours of hormone exposure. Additional evidence that thyroid hormone exerts a direct chronotropic effect on the heart can also be inferred from studies of the effects of sympatholytic agents in hyperthyroidism (9-12). In general, these studies demonstrated that the antiadrenergic agents decreased the tachycardia of hyperthyroidism but not to levels seen in normal, resting subjects. In addition, two studies failed to show any effects of antiadrenergic agents on the tachycardia of hyperthyroidism (28,29). Cairoli and Crout (19) studied the effect of combined sympathetic and parasympathetic blockade on the tachycardia of hyperthyroid rats. They found that atropine plus propranolol or atropine plus reserpine did not lower heart rate in the hyperthyroid animals to control levels. Thus, it seems clear that the tachycardia of hyperthyroidism results from both direct effects of thyroid hormone on the heart as well as excess adrenergic stimulation.

It also seems quite clear that excess thyroid hormone causes a direct enhancement of myocardial contractility. Buccino, et al (20) studied the effects of hyperthyroidism on the intrinsic mechanical properties of isolated cat papillary muscles. They found that hyperthyroidism caused an enhancement of the rate of isometric tension development, a decrease in the time required to reach peak tension, and a marked increase in the maximal velocity of muscle shortening at light loads. This increase in the contractile state of papillary muscles from hyperthyroid cats was not affected by depleting catecholamine stores in these cats by reserpine pretreatment (Figure 6). Similar findings were reported by Murayama and Goodkind (30) in isolated atria from hyperthyroid guinea pigs pretreated with reserpine. Using indices of myocardial contractility derived from external carotid pulse and phonocardiographic tracings, Amidi, et al (31) and Grossman, et al (32) found that neither reserpine nor sotalol (a cardiospecific beta-blocking agent) significantly altered the enhanced contractility present in hyperthyroid patients (Figures 7 and 8). These experimental and clinical findings generally agree that the alterations in the intrinsic contractile function of the heart in hyperthyroidism result almost entirely from a direct action of thyroid hormone on the heart. Adrenergic mechanisms apparently do not contribute significantly to the enhanced myocardial contractility of hyperthyroidism.

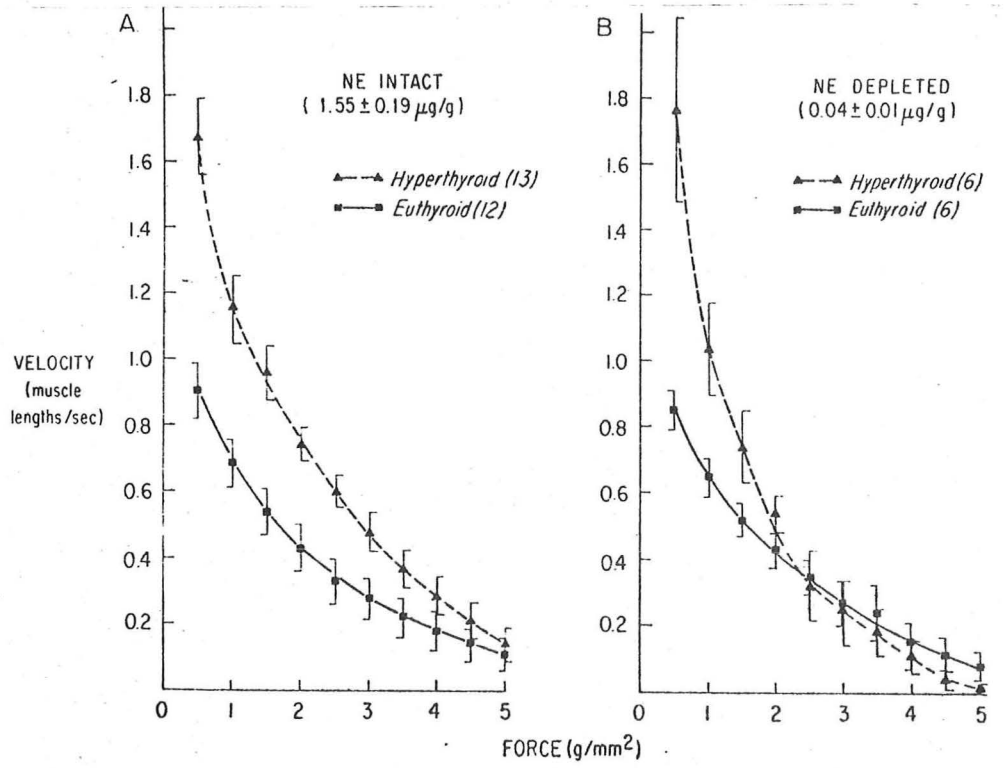

Figure 6
From Buccino, et al (20)

(A) The average force-velocity relationship for papillary muscles from 13 hyperthyroid and 12 euthyroid cats with intact cardiac norepinephrine stores. Right ventricular norepinephrine (NE) concentration is indicated in parentheses.

(B) The average force-velocity relationship for papillary muscles from six hyperthyroid and six euthyroid cats depleted of normal epinephrine by reserpine. Right ventricular norepinephrine concentration is indicated in parentheses.

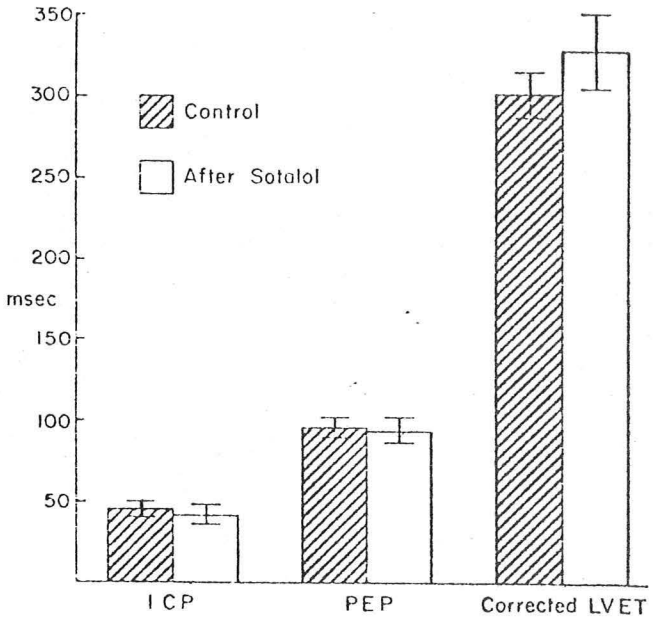

Figure 7
From Grossman, et al (32)

Systolic time intervals used as indices of myocardial contractility. Shaded bars represent measurements 10 min after intravenous sotalol (0.8 mg/kg body weight). Brackets indicate SEM. Changes were not statistically significant. ICP= isovolumic contraction period; PEP=pre-ejection period; corrected LVET= left ventricular ejection time corrected for heart rate.

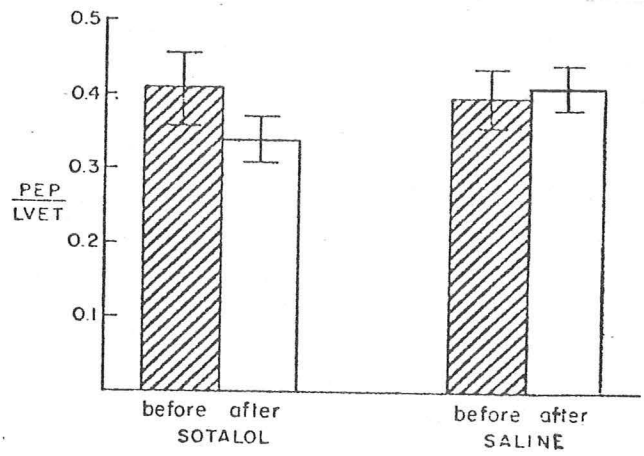

Figure 8
From Grossman, et al (32)

Ratio of pre-ejection period (PEP to left ventricular ejection time (LVET), used as an index of myocardial contractility. Representation is the same as in Figure 7. No statistically significant changes were noted.

The basic mechanism by which thyroid hormones exert their cardiotonic effects has been the subject of extensive investigation. The tachycardia characteristic of hyperthyroidism may well relate to an increased rate of diastolic depolarization and a decreased duration of the action potential in sinoatrial node cells. Such changes were consistently observed in a recent study of hyperthyroid rabbits (33) either in the presence or absence of propranolol (Figure 9). The increased probablity of arrhythmias in hyperthyroidism, particularly atrial fibrillation, may relate to the shortened refractory period and reduced electrical threshold which is observed in atrial cells in experimental hyperthyroidism (34).

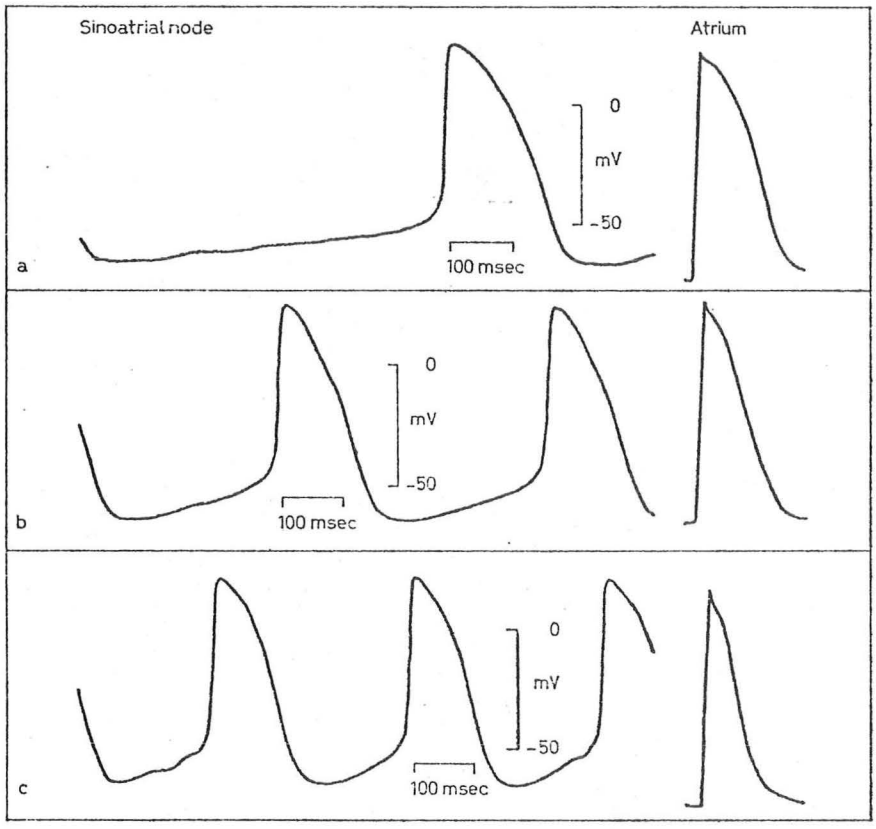

Figure 9
From Johnson, et al (33)

Transmembrane potentials from sinoatrial node and atrial muscle fibers in hypothyroid (a), euthyroid (b) and thyrotoxic (c) rabbit atria. The membrane potential and time calibrations apply to both sinoatrial node and atrium.

Mechanism of enhanced contractility

Several different modes of action have been proposed to explain the enhancement of myocardial contractility produced by excess thyroid hormone. Levey and Epstein (35) found that thyroid hormone caused an immediate rise in adenylate cyclase activity in particulate heart preparations from cats and man. This enzyme system is thought to mediate the positive inotropic effects of catecholamines and glucagon in the heart and could possibly explain the contractile effects of thyroid hormone. However, Skelton and co-workers (36) were unable to demonstrate an immediate effect of thyroid hormone on the contractile function of isolated cat papillary muscles (Figure 10), isolated guinea pig atria or the intact dog heart. Thyroxine administration for three days was required before definite alterations in contractility were observed in the cat. This delayed onset of action of thyroid hormone in vivo plus the repeated demonstration that adenylate cyclase levels in animals with induced hyperthyroidism were consistently low or normal (25) suggests that activation of adenylate cyclase is probably not an important factor in mediating the cardiotonic effects of excess thyroid hormone.

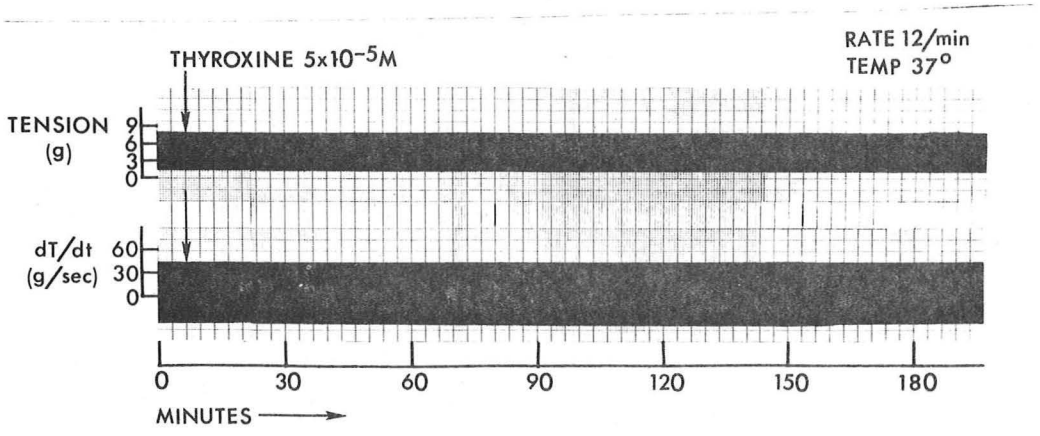

Figure 10
From Skelton, et al (36)

Effect of thyroxine ($5x10^{-5}M$) on representative isometrically contracting cat papillary muscle during observation period greater than 3 hours. dT/dt = rate of tension development.

Evidence implicating an action of thyroid hormone on cardiac sarcoplasmic reticulum has also been reported recently (37,38). Sarcoplasmic reticulum is an intracellular organelle with the capacity to accumulate and release calcium during the excitation-contraction-relaxation cycle of cardiac muscle. It probably serves as the major intracellular store for the contractile calcium which is released during depolarization of the cardiac cell. The sudden increase in intracellular calcium allows force generating cross-bridges to form between actin and myosin filaments resulting in muscle contraction. The sarcoplasmic reticulum also actively reaccumulates calcium to affect relaxation of the myofibril. In heart muscle from hyperthyroid dogs and rabbits, microsomes enriched with sarcoplasmic reticulum were found to accumulate and exchange calcium at an increased rate (37,38). Conditions which result in enhanced uptake and storage of calcium by sarcoplasmic reticulum probably result in increased availability of calcium to the myofibrils during activation as well as an enhanced rate of myofibrillar relaxation. Thus, alterations in the function of sarcoplasmic reticulum may be important in explaining the cardiac stimulatory effects of excess thyroid hormone.

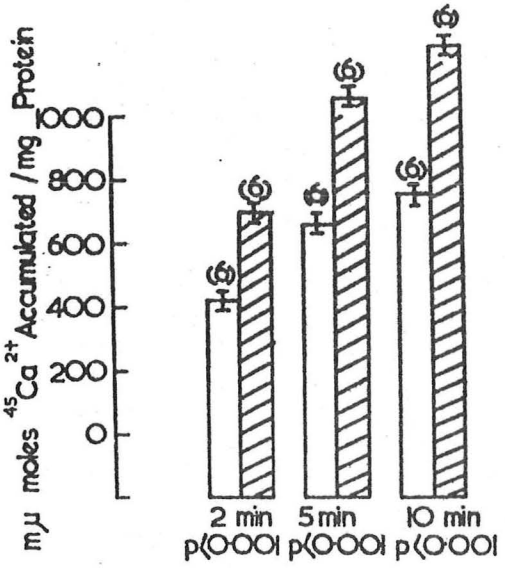

Figure 11
From Nayler, et al (37)

Comparison of the $^{45}Ca^{2+}$-accumulating activity of microsomal fractions isolated from control (euthyroid) and hyperthyroid heart muscle.

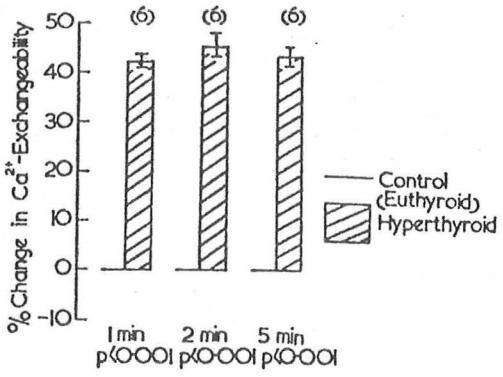

Figure 12
From Nayler, et al (37)

Effect of hyperthyroidism on the ability of dog cardiac microsomes to exchange $^{45}Ca^{2+}$. The results are expressed as a percentage change in $^{45}Ca^{2+}$ exchangeability, relative to the exchangeability found in microsomes prepared from euthyroid heart muscle.

Several studies have also suggested that alterations in the contractile proteins may mediate the myocardial effects of thyroid hormone. Enhanced myosin ATPase activity has been demonstrated in the hearts from hyperthyroid guinea pigs (39) and rabbits (40,41). The activity level of this enzyme is thought to regulate the rate of turnover of actin-myosin cross-bridge links in cardiac muscle, thereby directly influencing the maximal velocity of muscle shortening and rate of isometric tension development. These changes in myosin ATPase activity occurred gradually after thyroid hormone administration and the appearance of enhanced enzyme activity corresponded with the turnover rate of myosin (Table I).

Group	*n*	ATPase Activity (X 10^{-7}M Pi/mg protein-min)
Cardiac myosin		
Normal	16	8.15 ± 0.185
Thyroxine (1 day)	5	7.86 ± 0.211
Thyroxine (3 days)	5	7.56 ± 0.636
Thyroxine (8 days)	8	10.96 ± 0.686*
Thyroxine (21 days)	5	10.56 ± 0.401*
Cardiac myofibrils		
Normal	5	0.666 ± 0.0190
Thyroxine (8 days)	3	0.890 ± 0.0321*
Cardiac myofibrils with sodium azide (5 X 10^{-3}M)		
Normal	2	0.640
Thyroxine (8 days)	1	0.860

Table I
From Goodkind, et al (39)

Values are means ± 1 SE. *n* = the number of groups of animals studied; data from thyroxine-treated animals in each group are compared with results from normal controls. *$P \leq .001$.

Thyrum, et al (42) reported that the helical content and the amino acid composition of myosin isolated from hyperthyroid guinea pig hearts differed from that of normal controls. Thus, as might be predicted from our earlier discussion of the importance of protein synthesis in the basic mechanism of thyroid hormone action, it appears likely that thyroid hormone administration stimulates the synthesis of new cardiac myosin with altered enzymatic properties which may result in enhanced contractile capabilities.

Skelton, et al (43) have recently reported findings which provide indirect support for the importance of contractile protein changes in mediating the cardiac effects of thyroid hormone. Glycerinated papillary muscle strips from hyperthyroid rabbits were found to have an enhanced rate of tension development when exposed to an appropriate contraction solution. Sarcolemmal and sarcoplasmic reticular membrane function is largely eliminated by prolonged exposure to glycerine. Thus, it seems likely that the contractile changes noted in the glycerinated muscle strips from hyperthyroid rabbits resulted from a direct effect on the contractile proteins.

Cardiac Hypertrophy and Failure in Hyperthyroidism

Enlargement of the heart in hyperthyroidism has been recognized for over one hundred years. For a great many of these years a lively debate has continued as to whether excess thyroid hormone could induce cardiac enlargement or failure in the absence of other cardiac abnormalities. Even within the past 10 years it has been written that in uncomplicated hyperthyroidism in man, no hypertrophy of the heart occurs in the absence of complicating cardiac abnormalities (44,45). However, there is now a substantial body of evidence from many laboratories, including our own, that thyroid hormone excess leads to hypertrophy in a number of species and does so when the heart is perfectly normal at the onset (44-49). The degree of hypertrophy which occurs is usually not extreme, increases in left ventricular weight averaging 20% to 90%, depending on the duration of thyroid hormone administration. Interestingly, the cardiac hypertrophy induced by hyperthyroidism is completely reversible on discontinuation of thyroid hormone administration (49). Despite the development of cardiac hypertrophy, the contractile function of papillary muscles obtained from cats given excess thyroid hormone for 10 months remained enhanced, their contractile properties being similar to that characteristically seen in acute hyperthyroidism (10-14 days T_4 administration) (49) (Figure 13). These results are in marked contrast to the depressed contractile function seen in muscles removed from animals with right ventricular pressure overload or hereditary cardiomyopathy.

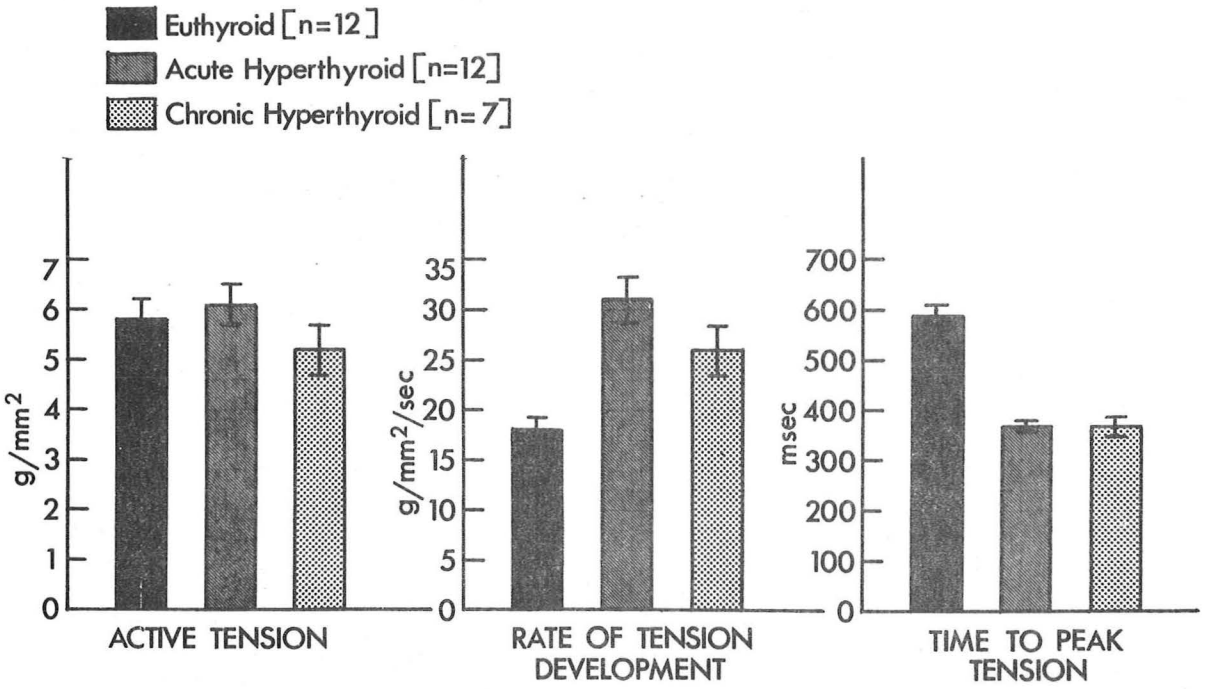

Figure 13
From Skelton, et al (49)

Isometric contractile function in papillary muscles from euthyroid cats and cats with acute (10 to 14 days) and chronic (10 months) hyperthyroidism.

In most experimental studies of thyroid hormone-induced cardiac hypertrophy, there was no progression to frank congestive heart failure. However, in the study reported by Piatnek-Leunissen and Olson (50) seven of thirty dogs treated with 1.2 mg/kg of thyroxine daily for an average of eight months developed objective signs of mild congestive failure as manifested by biventricular hypertrophy, elevated ventricular end-diastolic pressures, and varying degrees of passive congestion of the lungs and liver. Cardiac output remained elevated above normal levels in the dogs with failure but was slightly lower than the cardiac output in hyperthyroid dogs without congestive failure. These findings along with those cited previously provide strong experimental evidence that not only cardiac hypertrophy but also congestive failure can occur in hyperthyroidism in the absence of underlying cardiac abnormalities.

Documentation of cardiac hypertrophy and/or failure in man solely attributable to hyperthyroidism has been more difficult. In the frequently referenced paper by Likoff and Levine (51) which reported the occurrence of congestive heart failure in 21 patients with no demonstrable heart disease except thyrotoxicosis, complicating forms of heart disease were ruled out simply on the basis of history and physical examination. The absence of typical angina was accepted as evidence against coronary atherosclerotic disease. The fallacy of this assumption has been amply documented since the introduction of coronary arteriography. Similar criticisms can be made concerning many of the other reports purporting to show thyroid heart disease as a distinct entity (52-54). Perhaps the most objective evidence of thyroid-induced heart disease in man is the study of Sandler and Wilson (55) who found four patients at postmortem examination with cardiomegaly and/or congestive failure who had no pathologic evidence of complicating heart disease. Thus, despite less than adequate documentation in man, it seems likely that cardiac enlargement and even frank congestive heart failure may occur in a small percentage of patients solely on the basis of hyperthyroidism. More frequently, cardiac complications result when hyperthyroidism presents an added burden to a previously compromised heart, most often on the basis of coronary artery disease. In either case definitive therapy of the hyperthyroidism results in marked improvement of the cardiovascular status and hyperthyroidism should always be considered when treating patients with cardiac problems since it is a potentially curable form of heart disease.

The pathophysiologic basis of the cardiac abnormalities in hyperthyroidism is not clear. Histologic study of hearts from hyperthyroid patients and experimental animals have revealed no pattern unique for hyperthyroidism. Occasionally foci of lymphocytic and eosinophilic infiltration, mild fibrosis and fatty infiltration have been described along with hypertrophy of the myofibrils (25). Electron microscopic findings of significance have been largely confined to the mitochondria which are frequently increased in number and hypertrophied and contain localized areas of vacuolization and disorientation of the cristae (56). These changes are completely reversible when the experimental animal is allowed to return to the euthyroid state.

Several mechanisms may be postulated to explain the cardiac hypertrophy in hyperthyroidism. The well recognized circulatory changes, including a volume overload, an increase in contractility, and tachycardia all impose on the heart a demand for greater energy generation. Accelerated energy turnover, if sustained, may be read as a signal calling for an activation of synthetic processes leading to an adaptive growth response. Certain metabolic actions may also be important in this regard. Activation of protein synthetic processes by thyroid hormone (1) may stimulate cardiac cell growth directly. In addition, these synthetic processes themselves require energy and stimulate oxygen consumption which may trigger further

adaptive growth. Activation of membrane Na^+-K^+ ATPase (6) would also require increased oxygen consumption and energy utilization which might further stimulate adaptive growth. Any direct mitochondrial actions of thyroid hormone which accelerate respiration may have similar results (3,4). Finally, Skelton, et al (57) have shown that in hyperthyroid cats the high energy phosphates utilized during cardiac muscle contraction under controlled conditions is much greater than expected on the basis of the mechanical work performed (Table 2). Thus, in hyperthyroidism cardiac muscle uses energy inefficiently during contraction and this mechanochemical uncoupling may also stimulate adaptive growth.

	EUTHYROID	HYPERTHYROID	$\frac{\text{HYPERTHYROID}}{\text{EUTHYROID}} \times 100$
NO. OF CONTRACTIONS	25	25	100%
WORK PERFORMED g-cm/g	371	370	100%
~P USED μmoles/g	1.78	4.74	266%

Table 2
From Skelton, et al (57)

Comparative average values for contractile work and high energy phosphate (~ P) utilization in papillary muscles from euthyroid and hyperthyroid cats.

CLINICAL MANIFESTATIONS

Signs and Symptoms

Much of the symptomatology and clinical findings seen in hyperthyroid patients can be surmised from the physiologic alterations previously discussed. Palpitations, heart awareness, and occasionally dyspnea on exertion are usually the only cardiac symptoms in the younger age groups. In older patients, these symptoms are more pronounced and may be associated with the appearance of frank congestive heart failure and/or exacerbation of symptoms of associated heart disease, especially angina pectoris.

Physical examination of a typical patient with moderate to severe hyperthyroidism frequently reveals warm moist skin due to peripheral vasodilatation and augmented skin blood flow, increased pulse pressure, a resting tachycardia, brisk carotid pulsations, and a prominent suprasternal venous hum. Cardiac examination demonstrates an active apical impulse, an increased first heart sound, an accentuated pulmonic component of the second heart sound, an audible third heart sound, and a basal systolic murmur. Diastolic flow murmurs are heard on rare occasions which are probably mitral in origin. The well-known Means-Lerman systolic "scratch" or click is not commonly heard and is thought to be due to the rubbing together of normal pleural and pericardial surfaces because of the hyperdynamic heart and dilated pulmonary artery.

Assessment of the sleeping heart rate may be helpful in confirming the diagnosis of hyperthyroidism and in following the patient after initiation of therapy. Unlike euthyroid patients, there is little reduction in heart rate in thyrotoxic patients with sleep. A sleeping pulse rate of over 80 beats per minute makes the diagnosis of hyperthyroidism likely, particularly in older patients.

Electrocardiographic Findings

Considering the magnitude of the circulatory changes induced by hyperthyroidism, electrocardiographic changes are few. Sinus tachycardia and minor non-specific ST and T wave abnormalities are common but are nonspecific changes. Atrial fibrillation either paroxysmal or fixed occurs in approximately 15% of cases (58) and is the most important electrocardiographic abnormality in thyrotoxicosis. It is most often seen in patients with underlying heart disease but may also be present in uncomplicated thyrotoxicosis. Spontaneous reversion of atrial fibrillation to normal sinus rhythm is the rule after the patient is returned to a euthyroid status (59).

Less common ECG changes include voltage changes suggestive of LVH, notching and slurring of the P wave, P-R interval prolongation, Q-T interval shortening, and transient atrioventricular conduction abnormalities, including complete heart block (58-60).

Roentgenographic Findings

The chest x-ray is usually normal in uncomplicated thyrotoxicosis. Dilatation and increased pulsation of the pulmonary artery may occur probably secondary to increased pulmonary flow. Moderate cardiac enlargement is seen infrequently but when present it rarely returns to normal after effective antithyroid treatment (46). This probably is explained by the presence of concomitant cardiac disease since the moderate degrees of hypertrophy resulting from hyperthyroidism alone are probably not usually detected on the routine chest x-ray.

Apathetic Hyperthyroidism

The diagnosis of hyperthyroidism in elderly patients is frequently difficult because of the absence of typical hyperkinetic and ocular findings (61). A small group of elderly patients who are particularly difficult to identify on clinical grounds present an apathetic, placid facies suggesting myxedema rather than thyrotoxicosis (62). The salient clinical characteristics which help to identify a patient with apathetic thyrotoxicosis include:

1. Elderly patient with placid, apathetic facies.
2. Small goiter.
3. Presence of depression or lethargy.
4. Absence of usual thyrotoxic ocular manifestations.
5. Substantial muscular weakness and wasting.
6. Excessive weight loss.
7. Cardiovascular dysfunction with atrial fibrillation.

The identification of these apathetic patients is extremely important since they frequently present with severe cardiac dysfunction which is resistant to the usual modes of therapy. Dramatic improvement may result with initiation of appropriate antithyroid therapy.

TREATMENT OF THYROID HEART DISEASE

The object of therapy in the patient with heart disease and thyrotoxicosis is control of the hypermetabolism as soon as possible. Unfortunately, definitive medical therapy with either antithyroid drugs or radioactive iodine requires a long and variable period of time, usually several weeks to months. Therefore, therapeutic interventions which rapidly control the cardiac manifestations of hyperthyroidism before the onset of dire complications such as congestive heart failure are desirable in many patients and may be of critical importance in patients in the older age groups who frequently have coexisting atherosclerotic or hypertensive heart disease. Since many of the cardiac manifestations of thyrotoxicosis are partially the result of excessive adrenergic stimulation, immediate therapeutic efforts have recently been directed at interupting the adrenergic component in hyperthyroidism. The remainder of this presentation will primarily deal with this aspect of therapy. The reader is referred to standard texts for details of long-term antithyroid therapy with drugs or radioiodine.

Sympatholytic therapy in hyperthyroid patients with cardiac manifestations has primarily consisted of the use of reserpine, guanethidine, and propranolol. Each of these agents has been quite successful in ameliorating the tachycardia, palpitations, tremor, restlessness, muscle weakness, sweating, and heat intolerance of thyrotoxicosis (63-65). Reserpine and guanethidine also relieve lid lag and led retraction, whereas propranolol is ineffective in this regard. Reserpine and guanethidine have a slow onset of action which limits their applicability in acute situations such as thyroid storm and they both deplete tissues of catecholamines which may depress cardiovascular reflexes needed under stressful situations such as general anesthesia. Reserpine has the further disadvantage of occasionally causing severe mental depression in susceptible patients. Guanethidine therapy is frequently limited by the development of significant postural hypotension. In view of these limitations, propranolol has largely superceded reserpine and guanethidine in the adjunctive therapy of the adrenergic manifestations of hyperthyroidism.

Propranolol exerts its effects by competitively blocking beta adrenergic receptors in the heart and other tissues. This action does not result in tissue catecholamine depletion. The drug is rapidly effective either by the oral or intravenous route. The peak effect after oral administration occurs within 1 to 2 hours, with a half-life of approximately 3 hours (66). Intravenously, the peak effect is observed within minutes with an apparently biphasic half-life, one about 10 minutes and the other approximately 2 hours. The rapid onset of action of propranolol is a definite advantage in the early management of acutely ill patients with thyrotoxicosis. The oral dosage is variable but 40 to 160 mg daily in four divided doses generally is effective in relieving

the adrenergic manifestations of hyperthyroidism. Intravenous administration has been reserved for emergency situations such as thyrotoxic storm where 1 to 2 mg of propranolol may be given repeatedly over a fifteen minute period until symptomatic benefit is obtained (65). The effective dose of propranolol (usually less than 10 mg) may then be repeated after 4 to 6 hours until the emergency situation is resolved.

Propranolol is a myocardial depressent and is contraindicated in patients with the usual types of congestive heart failure. However, it is evident that many cases of cardiac failure in hyperthyroidism are rate related and propranolol would be useful under these circumstances despite the presence of heart failure. Before using propranolol in this situation, the patient should first be treated with the usual regimen for congestive heart failure including digitalis. Although hyperthyroid patients may be somewhat resistant to the effects of digitalis for reasons most likely involving such factors as absorption, distribution and metabolism, the drug should be given in effective doses. Following digitalization, propranolol may then be given either orally or intravenously under careful monitoring, preferably in an intensive care unit with all necessary personnel available to treat any untoward result. Under these conditions, it is possible to rapidly and safely determine whether heart rate reduction will improve congestive heart failure.

Despite its marked beneficial effect in hyperthyroidism, several parameters remain partially or completely unchanged after propranolol therapy. Although reports are conflicting (63-65), oxygen consumption remains elevated in most instances. Heart rate, cardiac index, and pulse pressure though markedly reduced by propranolol rarely return to basal levels. Weight loss appears to stabilize, but weight gain does not regularly occur. The size of the goiter remains unchanged since propranolol does not alter the basic etiologic stimulus to the thyroid gland which results in thyroid cell growth and excess thyroid hormone production. Serum cholesterol and thyroid function tests are not altered by propranolol. Thus, it is apparent that the basic metabolic abnormality in hyperthyroidism is not changed by propranolol and that it is mandatory to combine antiadrenergic therapy with definitive antithyroid therapy in the long-term management of thyrotoxicosis.

BIBLIOGRAPHY

1. Tata JR, Ernster L, Lindberg O, et al: The action of thyroid hormones at the cell level. Biochem J 86:408, 1963
2. Tata JR: Inhibition of the biological action of thyroid hormones by actinomycin D and puromycin. Nature (London) 197:1167, 1963
3. Sokoloff L: Action of thyroid hormones on protein synthesis as studied in isolated preparations and in the whole rat. In Proceedings of the Second International Congress of Endocrinology, edited S Taylor. Amsterdam, Excerpta Medica Foundation, 1965 p 87
4. Hoch FL: Energy Transformations in Mammals: Regulatory Mechanisms. Philadelphia, WB Saunders Co, 1971, p 83
5. Oppenheimer JH, Koerner D, Schwartz HL, et al: Specific nuclear triiodothyronine binding sites in rat liver and kidney. J Clin Endocrinol Metab 35:330, 1972
6. Ismail-Beigi F, Edelman I: Mechanism of thyroid calorigenesis: role of active sodium transport. Proc Nat Acad Sci 67:1071, 1970
7. Knight RA: The use of spinal anesthesia to control sympathetic overactivity in hyperthyroidism. Anesthesiology 6:225, 1945
8. Brewster WR Jr, Isaacs JR, Osgood PF, et al: The hemodynamic and metabolic interrelationships in the activity of epinephrine, norepinephrine, and the thyroid hormones. Circulation 13:1, 1956
9. Canary JJ, Schaff M, Duffy BJ Jr, et al: Effects of oral and intramuscular administration of reserpine in thyrotoxicosis. New Eng J Med 257:435, 1957

10. Waldstein SS, West GH Jr, Lee WY, et al: Guanethidine in hyperthyroidism. JAMA 189:609, 1964

11. Shanks RG, Hadden DR, Lowe DC, et al: Controlled trial of propranolol in thyrotoxicosis. Lancet 1:993, 1969

12. Howitt G, Rowlands DJ: Beta-sympathetic blockade in hyperthyroidism. Lancet 1:628, 1966

13. Harrison TS: Adrenal medullary and thyroid relationships. Physiol Rev 44:161, 1964

14. Waldstein SS: Thyroid-catecholamine interrelations. Ann Rev Med 17:123, 1966

15. Trendelenberg U: Supersensitivity and subsensitivity to sympathomimetic amines. Physiol Rev 15:225, 1963

16. Van der Schoot JB, Moran NC: An experimental evaluation of the reported influence of thyroxine on the cardiovascular effects of catecholamines. J Pharmacol Exp Ther 149:336, 1965

17. Moran NC, Van der Schoot JB: Thyroid-catecholamine interactions. In Factors Influencing Myocardial Contractility, edited by R Tang, F Kavaler, J Roberts, New York, Academic Press, 1967, p 603

18. Margolius HS, Gaffney TE: Effects of injected norepinephrine and sympathetic nerve stimulation in hypothyroid and hyperthyroid dogs. J Pharmacol Exp Ther 149:329, 1965

19. Cairoli VJ, Crout JR: Role of the autonomic nervous system in the resting tachycardia of experimental hyperthyroidism. J Pharmacol Exp Ther 158:55, 1967

20. Buccino RA, Spann JF Jr, Pool PE, et al: Influence of thyroid state on the intrinsic contractile properties and energy stores of the myocardium. J Clin Invest 46:1669, 1967

21. Levey GS, Skelton CL, Epstein SE: Influence of hyperthyroidism on the effects of norepinephrine on myocardial adenyl cyclase activity and contractile state. Endocrinology 85:1004, 1969

22. Wilson WR, Theilen EO, Hege JH, et al: Effects of beta adrenergic receptor blockade in normal subjects before, during, and after triiodothyronine-induced hypermetabolism. J Clin Invest 45:1159, 1966

23. Aoki VS, Wilson WR, Theilen EO, et al: The effects of triiodothyronine on hemodynamic responses to epinephrine and norepinephrine in man. J Pharmacol Exp Ther 157:62, 1967

24. Wildenthal K: Studies of isolated fetal mouse hearts in organ culture. J Clin Invest 51:2702, 1972

25. Levey GS: Catecholamine sensitivity, thyroid hormone and the heart. Amer J Med 50:413, 1971

26. Wurtman RJ, Kopin KJ, Axelrod J: Thyroid function and the cardiac disposition of catecholamines. Endocrinology 73:63, 1963

27. Markowitz C, Yater WM: Response of explanted cardiac muscle to thyroxine. Amer J Physiol 100:162, 1932

28. DeGroot WJ, Leonard JJ, Paley HW, et al: The importance of autonomic integrity in maintaining the hyperkinetic circulatory dynamics of human hyperthyroidism. J Clin Invest 40:1033, 1961

29. Wilson WR, Theilen EO, Fletcher FW: Pharmacodynamic effects

of beta adrenergic receptor blockade in patients with hyperthyroidism. J Clin Invest 43:1697, 1964

30. Murayama M, Goodkind MJ: Effect of thyroid hormone on the frequency-force relationship of atrial myocardium from the guinea pig. Circ Res 23:743, 1968

31. Amidi M, Leon DF, DeGroot WJ, et al: Effect of the thyroid state on myocardial contractility and ventricular ejection rate in man. Circulation 38:229, 1968

32. Grossman W, Robin NI, Johnson LW, et al: The enhanced myocardial contractility of thyrotoxicosis. Role of the beta adrenergic receptor. Ann Intern Med 74:869, 1971

33. Johnson PN, Freedberg AS, Marshall JM: Action of thyroid hormone on the transmembrane potentials from sinoatrial cells and atrial muscle cells in isolated atria of rabbits. Cardiology 58:273, 1973

34. Arnsdorf MF, Childers RW: Atrial electrophysiology in experimental hyperthyroidism in rabbits. Circ Res 26:575, 1970

35. Levey GS, Epstein SE: Myocardial adenyl cyclase: activation by thyroid hormones and evidence for two adenyl cyclase systems. J Clin Invest 48:1163, 1969

36. Skelton CL, Karch FE, Wildenthal K: Lack of acute effects of thyroid hormones on myocardial contractility. Amer J Physiol 224:957, 1973

37. Nayler WG, Merrillees NCR, Chipperfield D, et al: Influence of hyperthyroidism on the uptake and binding of calcium by

cardiac microsomal fractions and on mitochondrial structure. Cardiovasc Res 5:469, 1971

38. Suko J: The calcium pump of cardiac sarcoplasmic reticulum. Functional alterations at different levels of thyroid state in rabbits. J Physiol (London) 228:563, 1973
39. Goodkind MJ, Dambach GE, Thyrum PT, et al: Effect of thyroxine on ventricular myocardial contractility and ATPase activity in guinea pigs. Amer J Physiol 226:66, 1974
40. Yazaki Y, Raben MS: Effect of thyroid state on the enzymatic characteristics of cardiac myosin. Circ Res 36:208, 1975
41. Smitherman TC, Johnson RS, Richards EG: Cardiac hypertrophy in acute thyrotoxicosis: a new myosin? Clin Res 33:209a, 1975
42. Thyrum PT, Kritcher EM, Luchi RJ: Effect of l-thyroxine on the primary structure of cardiac myosin. Biochim Biophys Acta 197:335, 1970
43. Skelton CL, Su JY, Pool PE: Influence of hyperthyroidism on glycerol-extracted cardiac muscle from rabbits. Cardiovasc Res, in press
44. Wood P: Diseases of the Heart and Circulation, 3rd ed. Philadelphia, JB Lippincott Co, 1968, p 1008
45. Friedberg CK: Diseases of the Heart, 3rd ed. Philadelphia & London, WB Saunders Co, 1966, p 1615
46. Sandler G, Wilson GM: Production of cardiac hypertrophy by thyroxine in the rat. Quart J Exp Physiol 41:282, 1959

47. Beznak M: Cardiovascular effects of thyroxine treatment in normal rats. Canad J Biochem 40:1647, 1962

48. Cohen J, Aroesty JM, Rosenfeld MG: Determinants of thyroxine-induced cardiac hypertrophy in mice. Circ Res 18:388, 1966

49. Skelton CL, Sonnenblick EH: Heterogeneity of contractile function in cardiac hypertrophy. Circ Res 34 and 35 (Suppl II) 83, 1974

50. Piatnek-Leunissen D, Olson RE: Cardiac failure in the dog as a consequence of exogenous hyperthyroidism. Circ Res 20:242, 1967

51. Likoff WB, Levine SA: Thyrotoxicosis as the sole cause of heart failure. Amer J Med Sci 206:425, 1943

52. Graettinger JS, Muenster JJ, Selvorstone LA, et al: A correlation of clinical and hemodynamic studies in patients with hyperthyroidism with and without congestive heart failure. J Clin Invest 38:1316, 1959

53. Summers VK, Surtees SJ: Thyrotoxicosis and heart disease. Acta Med Scand 169:661, 1961

54. Goodman N: Thyrocardiac disease - fact or fancy. Dis Chest 49:188, 1966

55. Sandler G, Wilson GM: Nature and prognosis of heart disease in thyrotoxicosis. Quart J Med 28:347, 1959

56. Callas G, Hayes JR: Alterations in the fine structure of cardiac muscle mitochondria induced by hyperthyroidism. Anat Rec 178:539, 1974

57. Skelton CL, Pool PE, Seagren SC, et al: Mechanochemistry of cardiac muscle V: Influence of thyroid state on energy utilization. J Clin Invest 50:463, 1971

58. Hoffman I, Lowrey RD: The electrocardiogram in thyrotoxicosis. Amer J Cardiol 6:893, 1960

59. Teoh PC, Cheah JS, Chia BL: Effect of adrenergic blockade and specific antithyroid therapy on electrocardiographic changes in hyperthyroidism. Amer J Med Sci 268:157, 1974

60. Campus S, Rappelli A, Malavasi A, et al: Heart block and hyperthyroidism. Arch Intern Med 135:1091, 1975

61. Davis PJ, Davis FB: Hyperthyrodism in patients over the age of 60 years. Medicine 53:161, 1974

62. Thomas FB, Mazzaferri EL, Skillman TG: Apathetic thyrotoxicosis: a distinctive clinical and laboratory entity. Ann Int Med 72:679, 1970

63. Riddle MC, Schwartz TB: New tactics for hyperthyrodism: sympathetic blockade. Ann Int Med 72:749, 1970

64. Howitt G, Rowlands DJ: The heart in hyperthyroidism. Amer Heart J 73:282, 1967

65. Levey GS: The heart and hyperthyroidism. Med Clinics N.A. 59:193, 1975

66. Nies AS, Shand DG: Clinical pharmacology of propranolol. Circulation 52:6, 1975