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Blood pressure and circulatory dynamics in thyrotoxicosis

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BLOOD PRESSURE AND CIRCULATORY DYNAMICS IN THYROTOXICOSIS

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Thyrotoxic heart disease has come to be known as a type of chronic heart disease in which nearly complete recovery is possible with proper diagnostic and therapeutic handling. Thyrotoxic heart disease is often missed in diagnosis because it is seldom associated with the textbook signs of Graves' disease and because a causal goiter may not be conspicuous enough to attract the attention of patient or doctor. The condition is one whose presence must be constantly suspected in every case of heart disease, and indications of thyrotoxicosis--which may be minimal--must be sought for carefully and deliberately. Thyrotoxicosis should constitute an ever-present differential diagnosis in cardiology, as does syphilis in neurology. Consideration of thyrotoxic heart disease should include not only the actual cardiac manifestations, but also the types of thyrotoxicosis upon which the complication supervenes(1). Accurate diagnosis and proper treatment may well mean the difference between chronic invalidism and the restoration of health and a full life.

INCIDENCE

In the past some investigators have been unable to demonstrate any changes in blood pressure with thyrotoxicosis(2). Another group stated that the systolic blood pressure in primary thyrotoxicosis is in general

low(14)(15)(16). These earlier findings are far outweighed by opinions to the contrary with many authors stating that the blood pressure is often increased in thyrotoxicosis at certain stages of the disease, if not throughout(3)(4)(5)(6)(7)(17)(18). In recent years it has been emphasized repeatedly that these patients relatively often show an increased difference between the diastolic blood pressure and the systolic blood pressure(8)(9)(10)(11)(12). As an indication that thyrotoxicosis does influence blood pressure one author(3) presents an analysis of 265 thyroid cases who received subtotal thyroidectomy. He used 145mm. of mercury as the top limit of normal systolic pressure. Twenty six cases of this series had systolic pressures between 145 and 170mm. of mercury. Seventy three percent of these showed a decrease in systolic pressure one year after surgery. Fifty three percent of this group showed considerable reduction. In 9 cases the systolic pressure became normal. In a second group of 12 cases with systolic pressure of 170mm. of mercury or more 45% had a decrease of systolic pressure with maintenance of diastolic pressure for a period of one to five years. In 3 cases there was no change.

Using similar reasoning concerning the effect of thyrotoxicosis on blood pressure another investi ator (13) found that the systolic blood pressure prior to the operation of subtotal thyroidectomy, in about one half

the cases was higher than the normal maximum for persons in the respective age classes, and the remaining cases showed an amplitude equal to or a little lower than the normal level. On reexamination the systolic blood pressure had usually decreased somewhat and some of the excessively high values had fallen to a normal level.

In a series of 1000 consecutive cases of hyperthyroidism an investigator(20) found that 64 were hypertensive, 35 of these also having auricular fibrillation and 17 having congestive failure.

TYPES OF THYROTOXICOSIS AND RELATION TO ESSENTIAL HYPERTENSION

In general two types of hyperthyroidism are recognized. One type exists coincidentally with essential hypertension with this hypertension increased in severity by the abnormal thyroid condition. One group of writers(25) mention the fact that it has sometimes been thought that permanent essential hypertension might be a consequence of thyrotoxemia because of a specific effect on the vascular system. They further prophecy that because of the frequency of thyrotoxic hypertension, thyroid toxemia will some day be recognized as one of the sources of essential hypertension and not merely one of its concomitants.

The second type of hyperthyroidism isone which subtotal thyroidectomy relieves to a greater or lesser extent. One author(3) feels that the increased thyroid

activity precipitates or exaggerates a latent vascular disorder. He feels that the vessels may be able to carry a normal load but that increased metabolism produces an increased blood load which will not traverse the vessels without a pressure rise. This hypothesis he supports by the cold pressor test of Hines and Brown in which some of his patients having had subtotal thyroidectomies responded with pressures up to the pre-operative levels which stayed up longer and reduced slower than normal. Exercise caused the same rise and slow fall. It was assumed that these patients often had potential if not real hypertension with the latent factor precipitated or exaggerated by thyrotoxicosis.

The theory that hyperthyroidism may be accompanied by independent vascular hypertension is supported by another author(23). He finds the usual pulse pressure in this condition of hyperthyroidism to be less than but similar to that in aortic insufficiency with 160/75 not uncommon. Accompanying featuresof this condition were a capillary pulse, a Corrigan pulse, the pistol shot in the femoral artery, and Duroziez's sign.

Another manner in which to divide thyrotoxicosis is to call the one type primary thyrotoxicosis. This type is associated with Graves' disease. Secondary thyrotoxicosis is found associated with toxic nodular goiters. Thyrotoxic heart disease is much commoner in this secondary variety.

AGE DISTRI UTION OF THYROCARDIAC ST TE

One investigator(19) found the age distribution of 142 patients showing inclination of thyrocardi c state to occur in later life, and in hearts which were handicapped or crippled. His results are t bulated as follows:

AGE	NUMBER
20-29	1
30-39	17
40-49	37
50-59	56
60-69	27
70-75	4
	142

Another author(21) analyzed a series of 835 goiter cases from the Pacific Northwest states, chiefly from the standpoint of cardiac enlargement, cardiac fa lure, and auricular fibrillation in relation to a e incidence, basal metabolism, arterial hypertension, associated cardiopathies and the type of goiter present. Although cardiac failure and auricular fibri lation were seen usually as an accompaniment of advancing years, it was pointed out that they occured also before the age of thirty in goiter patients in whom other thyrogenic heart action and certain experimental evidence, sug ests the probability of specific thyroid eart lesions.

In a series of 432 cases from the Royal Free Hospital(22) it was seen that there was a tendency, as time went on, for the systolic pressure to rise without any corresponding increase in t e diastolic pressure. This ap lied to both types of thyrotoxicosis, the primary

toxic or exop thalmic goiter and the secondary toxic goiter or toxic adenoma, though in the secondary form the rise is rather greater after the age of fifty than it is in the primary form. The following table was prepared from this series:

Mean Blood Pressures According to Different Ages

	under 20	21-30	31-40	41-50	over 50
Primary toxic or exoph. goiter					
Systolic blood pressure. .	123	139	149	143	157
Diastolic blood press. . .	71	81	84	79	82
Pulse pressure	52	58	65	64	75
Secondary toxic goiter					
Systolic blood pressure. .	125	140	137	148	164
Diastolic blood press. . .	71	72	80	87	85
Pulse pressure	56	68	57	61	79

Another author(1) found that primary thyrotoxicosis occured typically in patients between 20 and 35 years, while secondary thyrotoxicosis was seldom found before the age of 40. Thyrotoxic heart disease was thought by this author to be very much commoner in the secondary variety and he regarded the difference to be so striking that it would be no exaggeration to regard primary thyrotoxicosis as a wasting disease and secondary thyrotoxicosis as a disease of the heart.

The main reason for this different incidence of thyrotoxic heart disease in the two types is, in his opinion, the different ages of the patients concerned. "Primary thyrotoxicosis occurs in young adults, whose hearts are better able to withstand the constant tachy-

cardia without breaking down. Thus auricular fibrillation and cardiac failure are rare--even in cases with long histories--but when they do occur some pre-existing cardiac lesion, such as rheumatic carditis, is often present. On the other hand, patients with secondary thyrotoxicosis are at or past middle age, and have thus had more chance to acquire rheumatic carditis, arteriosclerosis, or hypertension, and their hearts tend to break down into auricular fibrillation or failure within a comparatively short time."

SYMPTOMS AND DIAGNOSIS OF THYROCARDIAC STATE

A factor which affects the unequal age incidence of thyrotoxic heart disease in the two types of thyrotoxicosis lies in their different outward manifestations, which respectively help and hinder prompt diagnosis and treatment. Thus diagnosis cannot be long delayed after establishment of Graves' disease because of the striking clinical signs, and treatment is usually undertaken early. Helpful symptoms, clinical signs, and findings for the diagnosis of this condition include:

1. Loss of weight, associated with an adequate or excessive intake of food.
2. Increased tolerance to cold and decreased tolerance to heat.
3. Excessive perspiration and hyperemic skin.
4. Tachycardia, high pulse pressure, palpitation,

rapid circulation times, and at times irregularity of heart action and frank congestive failure.

6. Exophthalmos and allied ocular signs.
7. A peculiar psychomotor irritability or stimulation.
8. Gastro-intestinal crises.
9. Muscle weakness.
10. Usually firm, symmetrical enlargement of the thyroid gland.
11. Elevation of the basal metabolic rate.

On the other hand, the onset of secondary thyrotoxicosis is insidious and frequently unaccompanied by eye-signs, undue nervousness, or the other manifestations of Graves' disease. Moreover, the patients have often had a symptomless goiter for many years which they do not connect with the onset of cardiac symptoms, and they may not seek advice until auricular fibrillation or failurehave occured. Sometimes the goiter is incons icuous and the outward signs of thyrotoxicosis are minimal, in which case the thyrotoxicosis is termed "masked". The patients present cardiac symptoms, and close inquiry is needed to elicit a history of some weight loss, looseness of the bowels, or a little increase in nervousnessor sweating--which they often fail to volunteer. Specific inquiry must always be made for such symptoms, the neck must be carefully examined for the presence of thyroid enlargement or nodules, and, if necessary a basal metabolic rate be estimated.

One author(24) comments on the outstanding fact of the infrequency in both exophthalmic goiter and toxic adenoma of symptoms indicating cardiac disease. Only one fourth of the patients in his series of 377 cases had auricular fibrillation, and in less than one half of these was fibrillation a constant phenomenon; one fifth had evidence of slight cardiac weakness, a moderate degree of edema of the legs, which disappeared readily under tre tment with rest and digitalis. Not more than two percent of these patients had sufficient clinical evidence of myocardial injury to classify them as having serious cardiac disease.

An interesting point is made by a group of authors (25) in regard to the use of the basal metabolic rate as an aid in diagnosisi of thyrotoxic hypertension. In a patient with hypertension and a toxic goiter it must be remembered that the basal metabolic rate is often raised in hypertension itself, and especially if there is cardiac failure. A greater objection is that the basal metabolic rate may be normal with a toxic goiter.

These same authors presented a series of 100 patients with hypertension combined with thyrotoxicosis who had been observed over a period of four years. Their description of symptoms and findings reflects excellent investigative work and should aid considerably establishing criteria for the diagnosis of thyrotoxic

hypertension. Some of their findings are therefor included at this point:

"There were 91 females and 9 males. This striking disproportion is in contrast with what is usual in essential hypertension for there is generally only a moderate preponderance of females or none at all. The ages ranged from 22 to 74 years, but all except 8 were between 41 and 70 years."

"There was a previous history of a goiter in 68 cases, and in 33 of these it had been present for more than 15 years. In 32 there was good evidence that thyrotoxicosis had proceeded from the goiter in the past. Six had undergone a partial or subtotal thyroidectomy, but 5 of these had subsequently been thyrotoxic."

"Dyspnea and palpitation were the main cardiac symptoms, and in 23 the latter was based on auricular fibrillation--paroxysmal in 10 and permanent in 13. Symptoms referable to thyrotoxicosis were present in 94 patients, and of these the most important were weakness, loss of weight, nervousness, and tremor. A highly strung temperament, admitted by the patient, had significance. Local symptoms due to the goiter were uncommon; obstructive dyspnea was present in 5, and dysphagia in 5."

"All the patients in the series had established hypertension of not less than 160mm. of mercury systolic.

In 89 the diastolic pressure was 90mm. mercury or more. In those with auricular fibrillation, difficulty sometimes arose in deciding whether to admit a patient to the series. Blood pressure readings in fibrillation cannot compare for accuracy with those taken during normal rhythm, so these were never accepted as evidence in that small proportion seen only during fibrillation unless convincing figures were obtained."

"The association of tachycardia with the hypertension w as a striking feature and more than merely coincidental. In 7 it was ascribed to congestive heart failure. But in 66 of the remaining 93 patients a persistent tachycardia (i.e.,pulse rate over 90 per minute) prevailed although failure was absent. The tachycardia was slight(i.e., less than 100 per minute) in 21, moderate (i.e., from 100 to 120 per minute) in 36, and marked (i.e., over 120 per minute) in 9. There was collateral evidence of thyroid toxemia in all these cases. Tachycardia persisting for long periods in patients with hypertension, yet unaccompanied by heart failure, evidence a thyrotoxic factor."

"Extrasystoles were noted in 14 patients and confirmed by electrocardiogram in 10; they were of the ventricular type in 7, auricular in 2, and nodal in 1. Six of these cases had tachycardia also, with a pulse rate higher than 90 per minute. The incidence is not unusually high, so that extrasystoles in the presence of a high rate have little or no significance as an

index of thyrotoxicosis when there is no hypertension."

"Twenty-three patients in the series had auricular fibrillation; in 13 it was permanent and in 10 paroxysmal. This high incidence in a series of hypertensive patients is opposed to the usual retention of normal rhythm even when heart failure had supervened. Here the high incidence is attributable to thyrotoxicosis, and its importance is in relation to the premature induction of heart failure. Failure was present in 7 out of 100 cases, and 5 of these had permanent and 1 paroxysmal fibrillation. The effect of fibrillation was also shown by the left auricle which was seen to be enlarged(radiographically) only when auricular fibrillation had been present for some months. As fibrillation was related to thyroid toxemia in these cases, the contention of many that thyrotoxicosis itself does not lead to permanent changes in the heart is decidedly weakened. This enlargement of the left auricle was seen in 11 cases, 10 with permanent and 1 with paroxysmal auricular fibrillation. None had mitral stenosis, and rarely if ever was the auricular enlargement so disproportionate as in this condition. In two of three others who had established fibrillation without enlargement of the left auricle, the fibrillation was recent. In nine others who had paroxysmal auricular fibrillation without enlargement of the left auricle, the attacks had been infrequent

in all but two."

"There was other evidence on radiographs both of hypertension and of thyroid toxemia(cardiac). In 64 there was enlargement of the left ventricle and in 59 this was accompanied by uncoiling of the aorta. As is now recognized, hypertension produces an uncoiling or separation of the limbs of the aortic arch, as seen in the left oblique position by x-rays. The changes due directly to the goiter were shown by enlargement of the heart as a whole in 29, and of the pulmonary artery in 18; in 33 cases one or the other of these was present. In addition, there were the indirect effects of auricular fibrillation already mentioned. These observations show that the character of the cardiac enlargement in these patients is determined both by the hypertension and by the goiter, though the former predominates."

"General signs of thyrotoxicosis were present in 86 out of the 100 patients, the commonest being emotional unrest and nervousness of the type expected with thyroid toxemia, fine tremor, sweating or flushing, wasting, and exophthalmos. All these signs were present in 30 cases and at least 2 of them were found in 81; in the others the evidence of thyrotoxicosis was partial. These cases are exactly comparable with t e masked cases of ordinary hyperthyroidism, and they emphasize the frequency with which such incomplete forms ccur. In 14 patients eneral thyrotoxic signs were ab ent; but in addition to a goiter,

4 of these had paroxysmal auricular fibrillation, and in 4 the history of chronic goiter ranged from 14 to 40 years. Every patient in the series had enlargement of the gland except two who had under one a previous thyroidectomy. In 62 the enlargement was slight, in 34 moderate, and in 2 only it was great. The enlargement was general in 86, 4 of whom had adenomata in addition; the enlargement was purely adenomatous in 17. Eleven had a retrosternal goiter disclosed by x-ray examination."

RANGES OF SYSTOLIC AND DIASTOLIC PRESSURE AND PULSE PRESSURES

There is not complete agreement in the literature as to what can be expected of the blood pressure in thyrotoxic heart conditions. In general it is found that the systolic pressure rises somewhat and the diastolic pressure may rise with the systolic, or stay about the same, or fall. The difference among the various writers arise when they try to explain when and how hypertension occurs.

One author(22) attempts to explain the differences of opinion in the following way. He feels that there are differences in the stage of the disease at which the blood pressure estimations were made by various observers. This idea is supported by another writer(26) who points out that while in the early stages the blood pressure may be raised, it usually falls during a period of remission to rise again with the supervention of

cardiac hypertrophy. This generalization is probably subject to many exceptions, for in certain cases while the systolic pressure may be higher than normal the diastolic pressure is very little altered.

The pulse pressure is usually raised but one man(22) has met with cases in which it was not altered. Another writer(27) found that in both the primary and the secondary forms of thyrotoxicosis there is usually a raised systolic pressure with but little alteration in diastolic pressure, an increase in the pulse pressure thus resulting. The following table, prepared from his series of 432 cases, gives the figures. He feels that the tendency, as time goes on, is for the systolic pressure to rise without any corresponding increase in the diastolic pressure. He believes that these statements apply to both types of thyrotoxicosis, though in the secondary form the rise is rather greater after the age of fifty than it is in the primary form.

	Syst. B.P.			Diast. B.P.			Pulse Press.		
	Av.	High	Low	Av.	High	Low	Av.	High	Low
Exoph. goiter . .	144	200	100	81	110	60	59	110	30
Toxic adenoma . .	146	200	105	79	100	64	62	115	30

In another series the author(28) found that the systolic pressure was usually somewhat elevated in thyrotoxicosis with the average being 140-150. In from 25% to 33% of his cases the systolic pressure

exceeded 150. He found that the diastolic pressure was usually decreased with the average being 60-70mm. of mercury.

Another writer in a consecutive series of 377 patients with hyperthyroidism due to exophthalmic goiter or adenomatous goiter, found the pulse pressure increased beyond normal in both diseases. In his exophthalmic goiter patients the increase in pulse pressure was effected by a moderate increase in systolic pressure with normal or slightly lowered diastolic pressure. In his adenomatous goiter patients the systolic pressure with hyperthyroidism is greater with similarly greater diastolic pressure. He found that in adenomatous goiter distinctly higher diastolic blood pressures are more commonly encountered than in exophthalmic goiter.

	Outpatient		Entrance		Discharge	
	exoph.	aden.	exoph.	aden.	exoph.	aden.
Systolic.	147	153	131	139	128	129
Diastolic	73	83	72	78	75	76
Pulse pressure. .	74	70	59	61	53	53
Pulse rate. . . .	123	110	103	97	96	94

The above findings are in disagreement with the experience of another investigator(29) who had a series of 117 patients with toxic goiter. He recorded systolic blood pressure of 160mm. or above in 29 cases or 20%

and diastolic pressure 90mm. or above in 33 cases or 22%. He specifically disagrees with the findings of the previous author of increased pulse pressure. He did not find this to be the case in the early decades; but there was this tendency in the later decades, although even at that period it was not striking. He found that in adenoma the average diastolic pressure reached a peak at between forty and fifty years, which was also the peak of the age incidence of his series; and at the same period the highest average systolic pressures were recorded. He did not feel justified in making any general statement as to blood pressure in toxic goiter, other than that in toxic adenoma there does appear to be a substantial increase in the diastolic pressure.

In view of the constant elevation in basal metabolic rate in exophthalmic goiter and in adenomatous goiter with hyperthyroidism, it is obvious that there must be an increase in the rate of circulation to meet the increased demand of the tissues for the transportation of metabolites. The first effect of the increased demand is acceleration of the heart rate, soon followed by an increase in the volume outflow per beat. In the absence of aortic disease the increase in pulse pressure provided the diastolic pressure is not greatly increased, is evidence of this increased

output per beat. The rarity of an increased diastolic pressure in exophthalmic goiter shows that in this disease hypertension is not a common complication; on the other hand, the frequent observation of an increased diastolic pressure in adenomatous goiter with hyperthyroidism shows that this disease is often associated with hypertension.

CARDIOVASCULAR PATHOLOGY

The constant association of varying degrees of cardiac irregularity, observed in different grades of hyperthyroidism, has led to many clinical observations and studies of the morbid anatomy in an endeavor to ascertain the role of the secretory product (thyroxin) in the production of such disturbances. The characteristics of the increased volume output of the heart have been studied by several men(30)(31)(32)(33)(34)(35). These authors have concluded that the heart rate is proportionate to the degree of thyrotoxicosis. That as a result of the increased rate and volume outflow, in the presence of increased metabolism, the heart at first dilates and then hypertrophies. If the hyperthyroidism persisted, gallop rhythm, extrasystoles, fibrillation and finally dilatation occured. The question was raised as to whether such cardiac irregularities were attributable solely to thyroxin or to other factors such as age, the super-

imposition of thyrotoxicosis in the presence of arteriosclerosis of the coronary arteries or previously existing myocarditis. One man(36) believes there is s specific heart drive incited by thyrotoxicosis, while another(37) holds the opposite opinion pointing to the absence of specific pathological change in the hearts in such instances and the relative infrequency of cardiac irregularities in younger individuals as compared with those in middle or advanced age. A difference of opinion also exists as to the presence of specific changes in human hearts associated with hyperthyroidism.

One author(38) believes that fatty and parenchymatous degeneration, perivascular round cell infiltration, fibrosis and granulation tissue formation occurring in the hearts of instances of hyperthyroidism are specific. Another group of authors(21) suggest the probability of specific thyroid heart lesions since the cardiac failure and auricular fibrillation that are usually the accompaniment of advancing years, may also occur before the age of thirty in goiter patients in whom other thyrogenic heart action is evident.

To aid in clarification of the problem of myocardial damage the work of another group(39) proves of interest since they were able to show a difference in cardiac pathology between patients in the major groups of exophthalmic or primary thyrotoxicosis and adenoma-

tour or secondary thyrotoxicosis. Morphological study of hearts of 35 patients with exophthalmic goiter showed, with but few exceptions, no gross or microscopical pathological changes not equally represented in a carefully matched control series. The exceptions found were first a relatively higher incidence of myocardial fibrosis, endocardial sclerosis, and cellular infiltrations in the series with exophthalmic goiter and second, one case in the series of 35 which showed an active focal myocarditis for which no etiological factor can be ascertained other than the hyperthyroid state. Twenty eight, or 80% of the exophthalmic series showed areas of myocardial fibrosis, as compared with 51.5% of the control series. It was impossible to determine to what extent, if any, such areas of fibrosis may be the result of an active myocarditis of the type found in the single case. The hearts of 55 cases of adenomatous(nodular) goiter failed to show any significant difference in the incidence of pathological change as compared to a matched non-goitrous control series.

In an attempt to determine possible cardiac pathology due to thyrotoxicosis a group(40) used experimentally produced hyperthyroidism in rabbits with a control group and made a study of the pathology of the myocardium. There was no doubt about the majority of the rabbits in the groups having developed

a state of hyperthyroidism. The most striking evidence of hyperthyroid states in the rabbits was a loss of weight, increased pulse rate and a rise in blood pressure. It seemed to them fair to conclude that the speeding up of the metabolism lead directly or indirectly to an accelerated heart action which might eventually lead to cardiac exhaustion. The striking absence of comparable pathological changes in the hearts of control animals lead them to seriously consider cardiac damage in association with induced hyperthyroid states in rabbits. As to whether this change in the heart was due to the actual impingment of thyroxin upon the cardiac circulation or musculature was difficult to determine. It seemed to be a well established fact that metabolism is progressively and proportionately stimulated as a result of which the major body processes are augmented. Nutritional imbalance naturally would follow. The glycogen reserve of the liver as well as in the heart finally would become exhausted. As this proceeds there would occur increased oxygen consumption and the increased transportation of metabolites would lead to the necessity of adjustment on the part of the circulation. There would follow an increased pulse rate, augmented cardiac outflow, enlargement of the vascular bed and increased blood volume. It would be reasonable to conceive that the extra load

placed upon the heart eventually might lead to fatigue and failure.

The experimentally produced hyperthyroidism in these rabbits for a period of 23 days resulted in the following changes in the hearts: parenchymatous and fatty degeneration, histiocyte invasion, fraying of the muscle bundles and early fibrosis. It was believed possible that similar changes might be produced by cardiac overwork irrespective of the presence of an excess of thyroxin in the circulating blood as was indicated by the results obtained by cutting of the depressor nerves and denuding the carotid sinuses of their investments in order to allow the heart to operate uncontrolled.

There is evidence in the literature to disprove the fact that a heart, that is induced to work more rapidly, with an increased volume output in the presence of increased pressure and metabolism(as is true in hyperthyroidism) may not exhaust its nutrition and respond with morbid anatomical impingement of thyroxin on the myocardium.

In general experimentally produced hyperthyroidism has been rather unsuccessful in solving the problem of the heart lesions in hyperthyroidism. One group (41)(42)(43) working with various animals was able to produce histiocytes, round cells, perivascular necrosis

and fibrosis in the heart muscle. Others, on the other hand(44)(45) were not able to demonstrate specific lesions in the hearts of such experimental amimals.

Two other authors(46)(47) are in agreement with the theory that in the hyperthyroid group cardiovascular damage consists chiefly in a functional disturbance rather than a structural change. They cite the fact that almost all the hyperthyroid patients with cardiac damage were older than those without damage. They believe the high incidence of arteriosclerosis in this group suggests that hyperthyroidism per se is not responsible for the so-called thyroid heart disease, but produces functional disturbance in a previously damaged cardiovascular system.

CARDIOVASCULAR PHYSIOLOGY

An interesting description is presented by two authors(45) regarding the physiological explanation for myocardial damage in thyrotoxicosis. They summarize theories that have been presented above in the section on pathology regarding the possibility of a toxin circulating in the blood causing the damage or, on the other hand, of physiological wear and tear due to excess myocardial activity. They conclude that present evidence points against toxins producing specific myocardial damage. Instead they call attention to the general neglect of important alterations in the metabolism and function of the muscle fibers. In this con-

nection attention was drawn to the recent work on the glycogen content of voluntary and cardiac mucslce in hyperthyroidism. It had been shown that in the experimentally produced disease no glycogen could be found microscopically or by analysis in the myocardium. As a result of this, rigor mortis would set in immediately. It was well known that the withdrawal of glycogen from cells normally well supplied with it renders them more liable to injury, injury to which they react by diminished function and actual structural change and death. This problem had been well examined in the case of the liver and they thought one might well believe that similar reasoning could be applied to the myocardium. It seems more than probable that a close examination of this and other physiological problems will bring one nearer to the understanding of the cardiac abnormalities in hyperthyroidism.

Another investigator(46) conducted experiments on animals in which he administered thyroxin to rabbits and guinea pigs and was able to alter the metabolism of the myocardium so that:

a. The heart beat at an enhanced rate for hours after isolation.

b. The oxygen consumption of the heart was increased, and,

c. The glycogen content of the cardiac muscle was diminished.

The third finding is in accord with the above described theory on glycogen metabolism.

The significant physiology related to the production of pulse pressure variations, to the correlation between elevated pulse rates and increased metabolism and correlation of clinical manifestations with changes in venous and arterial pressures is presented by two groups of authors (47)(48). The information presented by these workers is summarized in the following explanation:

The work done by the heart consists mainly in expelling the blood into the aorta and into the pulmonary artery against the existing pressures and in imparting to the blood a certain velocity. The conspicuously increased velocity of blood flow found in patients with thyrotoxicosis emphasizes the strain under which the heart labors even when the body is under basal metabolic conditions.

Certain facts assume increased significance when considered in relation to the results obtained. The hot, flushed, salmon-colored skin, the tendency to perspire, the increased pulse pressure, the tendency to increased blood volume and the diminution in vital capacity of the lungs observed clinically suggest that considerable vasodilatation is present in thyrotoxicosis and

that the functional cross sectional diameter of peripheral and pulmonary vascular beds is increased. If other factors remain equal, an increase in functional cross sectional area of the vascular bed would tend to diminish the speed of blood flow. The fact that the velocity of blood flow is so strikingly increased in spite of the existence of considerable vasodilatation is further evidence of the extreme strain under which the heart labors.

Increased tissue metabolism cannot take place unless there is proportionate increase both in blood flow and in effective pulmonary ventilation.

The extremely rapid velocity of blood flow observed in patients with thyrotoxicosis affords additional information as to why such individuals experience signs and symptoms of circulatory insufficiency on but relatively slight exertion. It has been shown that a given amount of work by thyrotoxic patients is accompanied by a disproportionate rise in basal metabolic rate requiring s similar disproportionate rise in ventilation and in blood flow. The vital capacity of thyrotoxics is reduced thus overloading the heart further.

TREATMENT AND PROGNOSIS OF THYROTOXIC CARDIAC DISEASE

The hearts of patients with exophthalmic

goiter and adenomatous goiter with hyperthyroidism are subjected to tremendous demands--demands far in excess of those made in any other disease; in consequence it is incumbent on the physician and the surgeon to aid the heart by appropriate measures of treatment.

Subtotal thyroidectomy is the treatment of choice. The results are excellent even in cases in which the patient at first appears to be a hopeless cardiac invalid. Patients should not be operated on, however, until cardiac function has been restored, and for this purpose the mercurial diuretics are of the greatest value. Although digitalis may be necessary in some cases, it should be used with caution. One author(49) has stated that administration of digitalis decreases the output of the heart with hypertension. Auricular fibrillation occasionally persists after relief of hyperthyroidism, but in most instances there is a spontaneous return to normal cardiac rhythm.

After subtotal thyroidectomy for adenomatous goiter, recurrence of adenomatous tissue takes place very rarely. Since exophthalmic goiter cannot always be distinguished clinically from adenomatous goiter with hyperthyroidism, compound solution of iodine(Lugol's solution) should usually be given prior to operation in all cases of hyperthyroidism even though diagnostic criteria clearly point to a hyper-functioning adenomatous goiter.

It is possible to control the hyperthyroidism associated with adenomatous goiter with drugs such as thiouracil, thiourea, and propylthiouracil. Clinical response to such medication often takes place much more slowly than when exophthalmic goiter is treated by this means. Moreover, in nodular goiter it is impossible to be sure on clinical grounds that malignant change is not present or may not occur. On this account it is probably unwise to withhold surgical treatment in such cases.

In reporting mortality from surgery one writer(19) with 138 operated thyrocardiacs, 93 of whom were in varying degrees of congestive failure, had 5 deaths or 3.6%. The average history of symptoms(heart) before operation was two and one half years; the average period during which the patients had been well and active after operation was three and one half years. Every thyrocardiac coming to the clinic was operated and all with general anesthetic, indicating that there were essentially no thyrocardiacs who were too decompensated to withstand subtotal thyroidectomy without an undue risk. Of the 101 patients traced, and living, an average of three and one half years after operation, but two were completely disabled, four partially disabled, ninety-five were returned to the full function which they possessed before the onset of hyperthyroidism.

Another surgeon(3) reports a series of 265 cases

who received subtotal thyroidectomies. He used 145mm. of mercury as the top limit of normal systolic pressure. Twenty-six of these cases had pressure ranging from 145-170mm. of mercury. Seventy-three per cent of these showed decreased systolic pressure one year after surgery, 53% showed considerable reduction. In 9 cases the pressure became normal. In a second group of 12 cases with systolic pressure of 170mm. of mercury or more 45% of these had decreased systolic and diastolic pressures maintained one to five years. In 3 cases the pressure increased, in 2 an extreme increase was noted, and in 2 cases there was no change.

These favorable results are at variance with the results of another writer(29) with a series of 117 cases. He had a large number (46%) of individuals in whom the condition after operation, with a resultant drop in the basal rate, was either not improved or was doubtful, and in whom the pulse rate remained somewhat elevated(above 90 in 33 cases) and dyspnea of some degree persisted. He believed that this strongly suggested that the heart had not fully recovered from the toxic insult it had sustained.

MORTALITY ASSOCIATED WITH HYPERTHYROIDISM

One writer(46) in discussing mortality had a series of 200 cases of hyperthyroidism in which congestive heart failure was said to have occurred in 18.5%. The average duration of symptoms was conspicuously

greater in the cases with myocardial insufficiency. Its incidence increased in the age decades above forty and was most common, in any age group, in association with other, pre-existent factors which tend to diminish the cardiac reserve; rheumatic heart disease, hypertension, arteriosclerosis or, more rarely, syphilitic heart disease.

Another group(24) is somewhat in disagreement with the above remarks. In a series of 23 deaths, including postoperative cases, there was, in their opinion, one in which the heart could be considered as a major contributory cause. They recounted how deaths from postoperative acute hyperthyroid crisis with increasing elevation of the heart rate with or without the development of auricular fibrillation, have, as a rule, been considered by the surgeon as due to heart failure. They felt that careful analysis of the symptoms in their series of cases revealed that such an interpretation of death was not in the main justified except for the final cataclysm. The evidence pointed to the reverse conclusion, reasoning that the increased heart rate was an expression of the attempt of the heart to increase its volume output sufficiently to meet the demands made on it by the greatly increased metabolism. They felt that the heart muscle, like other tissue in the body, was rendered more irritable and less efficient by the intense thyroid intoxication.

From the study of the various data and from an analysis of the individual case reports, especially of patients who died, the conclusion was made that if the patient was properly treated, cardiac death in exophthalmic goiter and in adenomatous goiter with hyperthyroidism was a very rare occurrence.

SUMMARY

A review of the literature is presented regarding the blood pressure and the circulatory dynamics in thyrotoxicosis. It has been shown that there are important effects on the blood pressure and the cardiovascular system produced by thyrotoxicosis. The types of thyrotoxicosis and their relation to essential hypertension were described. There is a discussion of the age distribution and mean blood pressures according to different ages. The symptoms and methods of diagnosis of the condition are indicated. The average ranges of systolic and diastolic pressures and pulse pressures are given. There is a discussion of cardiovascular pathology and physiology. Treatment and prognosis of thyrotoxic cardiac disease is discussed. The mortality associated with hyperthyroidism is reviewed briefly.

CONCLUSIONS

Thyrotoxic heart disease has come to be known as a type of chronic heart disease in which nearly complete recovery is possible with proper diagnosis and treatment. Thyrotoxic heart disease is often missed in diagnosis. The condition is one which must be constantly

suspected in every case of heart disease. Accurate diagnosis and proper treatment may mean the difference between chronic invalidism and restoration of health.

It has been established that there are blood pressure changes with thyrotoxicosis, with findings of an increase in systolic pressure and varying changes in diastolic pressure.

Two types of hyperthyroidism are recognized. One type exists coincidentally with essential hypertension, with this hypertension increased by the abnormal thyroid activity. The second type is often relieved by thyroidectomy and may be an exaggeration of a latent vascular disorder. Thyrotoxicosis is further classified into the primary type associated with Graves' disease and the secondary type associated with toxic nodular goiters.

The thyrocardiac state is shown to produce greater hypertension with advancing age with secondary thyrotoxicosis producing a higher systolic pressure after age fifty than primary thyrotoxicosis and diastolic pressure, in general, not rising with the systolic pressure. Many believe secondary thyrotoxicosis to be a disease of the heart since it occurs in older people with weaker hearts less able to withstand the constant excessive demands than the hearts of younger people.

Primary thyrotoxicosis is usually diagnosed early since it is accompanied by the many and unmistakeable signs of Graves' disease. Secondary thyrotoxicosis is

insidious and often unaccompanied by outstanding signs and symptoms. Close inquiry is therefor required to elicit a history that will point toward the thyroid gland as the cause of the cardiac condition. Symptoms and findings seldom or often associated with thyrotoxicosis include: a previous history of goiter, dyspnea, palpitation, hypertension, tachycardia, extrasystoles, auricular fibrillation, left ventricular enlargement, uncoiling of the limbs of the aortic arch, and general signs of thyrotoxicosis such as emotional unrest, nervousness, fine tremor, sweating, flushing, wasting and exophthalmous.

There is disagreement concerning the ranges of systolic and diastolic pressures and pulse pressures. In general most writers feel that there is a rise in systolic pressure with the diastolic pressure remaining the same or dropping a little. Averages for diastolic pressure are given variously from 70 to 83mm. of mercury. Systolic pressures average 145 to 160mm. of mercury, with somewhat higher pressures being developed in secondary thyrotoxicosis. Pulse pressures average 60 to 75mm. of mercury.

Some investigators feel that they can demonstrate specific cardiac pathology while others disagree completely. One group believed that it had produced tissue changes in rabbits with experimentally produced thyrotoxicosis.

The physiological aspects of thyrotoxicosis evolve around three major theories. One theory puts forth the possibility of a specific toxin circulating in the blood causing myocardial damage. Another theory is centered about the increased metabolism of the whole body caused by excessive thyroid activity producing excessive wear and tear on the myocardium as that organ takes part in the speeded up body processes. The third theory advanced maintains that excessive metabolism depletes the myocardium of glycogen below an optimum level rendering the tissues more liable to injury. The heart labors under considerable strain since even though general vasodilatation has increased the functional cross section of the vessels, the velocity of blood flow is increased.

Subtotal thyroidectomy is the treatment of choice. The results are excellent even in cases in which the patient at first appears to be a hopeless cardiac invalid. Operation should not be performed until cardiac function has been restored. Mercurial diuretics are useful for this purpose. Digitalis is also useful but must be administered with caution since the output of a hypertensive heart may be decreased. Lugol's solution should be given pre-operatively since exophthalmic goiter cannot always be distinguished from a hyperfunctioning adenomatous goiter. Secondary thyrotoxicosis may be controlled by the use of thiouracil, thiourea,

and propylthiouracil but results are slow compared to exophthalmic goiter. Since it is impossible to be sure on clinical grounds that malignant change is not present it is probably unwise to withhold surgical treatment.

Mortality averages about 3.5% from surgical treatment. Seventy to ninety-eight per cent of patients are benefited wholly or in part by such treatment.

Cardiac death in both primary and secondary thyrotoxicosis seems to be a rare occurrence in properly treated patients.

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