The Thyroid and the Circulation

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Generally speaking, practical knowledge of thyroid function and its circulatory consequences in health and disease has advanced by several stages. The significance of hyperthyroidism as a form of circulatory stress was recognized 165 years ago by Parry, though his descriptions were not published until 1825. Comprehension of the manifestations of hypothyroidism emerged from the early attempts to treat thyrotoxicosis by excision of the gland. The effectiveness of substitution therapy in treating myxedema was discovered in 1891 but suppression of the overactive thyroid by drugs, first with iodine, later and more effectively by thiourea derivatives, was not accomplished until several decades later. Most recently, interest has centered upon the ability of derivatives of thiourea and radio- active iodine to reduce the function of the normal thyroid gland, a property which has been grasped as a therapeutic tool in the treatment of intractable heart failure in euthyroid persons.

Particularly since the thyroid principle has been available in an injectable form, attention has been devoted to the special effects of induced hyperthyroidism upon other physiologic functions including those of the heart and circulation. Tachycardia and increased cardiac output at rest,1,2 exaggerated by exertion or excitement,3 regularly follow thyroid feeding or the injection of thyroxin in animals but only after a latent period of 7 to 24 hours. Moreover, this effect may be produced in the embryo before the heart has been innervated4 or in the heart of one animal transplanted into the neck of another when the typical effects of thyroxin are produced in the host.5 Thyroxin has been shown to increase the rate of beating of explanted cardiac muscle cells from 2 day old chick embryos but only after 12 hours contact with the tissue.6 Tachycardia, once provoked in the intact animal by thyroid feeding or thyroxin injection, persists in the isolated perfused heart and increases far more than normal on addition of adrenaline to the perfusate.7 The denervated heart in situ in a hyperthyroid animal displays an exaggerated response to exercise or injected adrenaline.

The oxygen consumption of the heart-lung preparation from thyroxinized animals is measurably increased8 as is the oxygen uptake of the isolated auricles from thyroxinized guinea pigs.9 It has been debated whether the increased rate of oxygen consumption can be accounted for by the increased heart rate. In the heart-lung preparation it seems that this may be so, but the oxygen consumption of the isolated auricle is measurably increased even though it fails to contract. In a few instances the oxygen consumption of that portion of the human heart drained by the coronary sinus (left ventricle) has been estimated by catheterization in the presence of hyperthyroidism, and found not to be notably abnormal. In experimental hyperthyroidism, however, it seems certain that the cardiac tissue shares in the metabolic effect of the thyroid hormone, and that the tachycardia characteristic of thyroid action is due to a direct effect of the hormone, perhaps metabolic in nature, upon the heart itself.10 In contrast, dinitrophenol, which notably stimulates metabolism, has much less influence on heart rate or none at all.

The nature of the metabolic action of thyroxin upon the body tissues is not precisely known but it can be shown to persist in an

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aqueous enzyme-containing extract of the muscle of thyroxinized animals and may, therefore, involve a change in the amount or potency of tissue enzymes.\textsuperscript{11} Recent studies\textsuperscript{12, 13} suggest that, by inhibiting certain enzymes which catalyze the anaerobic synthesis of high-energy phosphate compounds, thyroxin forces the metabolism of muscle into aerobic channels, requiring greater direct consumption of oxygen.

The hearts of thyroid-fed animals are heavier in proportion to body weight than those of normal controls. Because microscopic changes —intermuscular fibrosis or cellular infiltration —have been described in the hearts of some patients dying with thyrotoxicosis, the concept has been widely held in the past that in hyperthyroidism the excessive thyroid secretion exerts a specific degenerative action upon the myocardium. Rather, it seems probable that the metabolic action of thyroxin may lay the myocardium open to other nonspecific forms of injury by depleting its chemical stores. In the absence of other coexisting forms of heart disease, the changes observed are rarely significantly different in kind or degree from those in hearts of patients dying from other unrelated diseases. Goodpasture,\textsuperscript{14} whose report of two cases is frequently referred to as indicating specific injury of the heart by hyperthyroidism, actually held the alternative view. After demonstrating that thyroxin rendered the hearts of animals unusually susceptible to injury by chloroform, he concluded that: "The evidence does not indicate that products of the thyroid alone could be responsible for the cardiac lesions which may occasionally occur in man in association with hyperthyroidism."

The overactive heart is a familiar accompaniment of hyperthyroidism in man. In many significant respects the circulation in such a patient at rest resembles that of a normal person after strenuous exercise. The heart rate is increased, the cardiac impulses are diffuse and forceful, the pulse pressure is widened and the skin capillaries are opened; the cardiac output is augmented and the entire circulation accelerated in response to the greater demands for blood created by the increased metabolic rate of the whole body. When patients with hyperthyroidism do undertake exercise, their circulatory reaction is extravagant as compared with normal persons performing the same work. In the presence of thyrotoxicosis, blood lactic acid rises excessively with effort and falls more gradually to the resting level.

The augmented circulatory demands in other tissues increase the work of the heart and the effect of excess circulating thyroid hormone seems to exaggerate the metabolic cost of that work. If not relieved by measures which diminish the output of thyroid hormone and reduce the metabolic rate, the circulatory burden may, in some instances, overwhelm the heart, provoking myocardial insufficiency. Especially remarkable, however, is the fact that, unless the cardiac reserve has already been diminished by disease, or by the natural processes of aging, the load upon the myocardium rarely becomes intolerable. The otherwise healthy hearts of persons less than 40 years of age bear the exorbitant circulatory demands of hyperthyroidism without signs of failure. In older patients, on the other hand, myocardial insufficiency may develop. This is especially true in cases of adenomatous goiter with hyperthyroidism, in which the circulatory strain, though often insidious, is frequently more protracted than in the more stormy instances of exophthalmic goiter in younger persons.

It is not surprising that the consequences of arteriosclerosis in terms of local circulatory deficiency are notably exaggerated in patients with hyperthyroidism. Angina pectoris occurs under these circumstances, and abates when the overactivity of the thyroid is curbed by appropriate therapy. In rare instances severe circulatory insufficiency in the feet, even impending gangrene, has been observed in the presence of thyrotoxicosis and relieved by iodine therapy and subtotal thyroidectomy. The circulatory requirements of the heart muscle, or of the legs, in these cases have evidently been augmented beyond the capacity of the available blood vessels by excessive thyroid secretion; when this is reduced the tissue demands can be met by the supply.

Auricular fibrillation is a common accompaniment of hyperthyroidism particularly in middle age and after. Occurring in paroxysms,
it may be the presenting symptom of thyrotoxicosis in these patients. Indeed, this irregularity, with symptoms and signs of cardiac failure, may overshadow the underlying hyperthyroidism. If the basic abnormality is searched out and appropriately treated, the results are frequently dramatic. If, on the other hand, thyrotoxicosis remains unrecognized, treatment of the cardiac status is relatively unrewarding. As an established arrhythmia, auricular fibrillation is present in over half the hyperthyroid patients with cardiac failure. Probably arising as a manifestation of increased excitability of the auricular musculature, auricular fibrillation is notably resistant to treatment in the presence of hyperthyroidism until effective measures have been taken to reduce the excess of circulating thyroid hormone.

The functional effects of the lack of thyroid hormone upon tissue metabolism are not yet completely elucidated, but it has been shown that certain tissue enzymes are decreased in amount or potency.15 The isolated hearts of thyroidectomized animals react sluggishly to adrenaline,16 and their denervated hearts in situ respond to exercise or to injected adrenaline with less acceleration than the normal. The normal reactivity is restored in these animals when metabolism is raised to normal levels with thyroxin.17 Responsiveness to a variety of vasoactive drugs—adrenaline, noradrenaline, renin and angiotonin—is diminished in hypothyroid dogs with normal blood pressure, but not in animals with hypertension.18 Capillary permeability, on the other hand, is notably increased in myxedema.19

In myxedematous animals the water content of the myocardium is significantly augmented and the muscle fibers show distinct degenerative changes. Gross abnormalities in the human heart in myxedema were first noted by Ord in 1880.20 A few years later (1888) a committee of the Clinical Society of London reported on 20 autopsied cases of untreated myxedema. The hearts were examined in nine of these. One showed an early stage of interstitial myocarditis and another a comparatively advanced degree of the same.

Since the treatment of myxedema with thyroid substance was begun in 1891, only a few reports are available of detailed pathologic study of hearts of patients dying of hypothyroidism. These describe swelling of the heart muscle fibers, their sarcoplasm partly replaced by slightly granular basophilic material, and interstitial edema. Myocardial fibrosis and hypertrophy when encountered in such cases are now usually ascribed to other accompanying cardiac or vascular disease.

The cardiac enlargement often observed in these instances, which proves to be readily reversible by adequate doses of thyroid extract, unless another form of heart disease is also present, does not evidently represent true hypertrophy but rather myxedema of the heart muscle. Pericardial effusion, sometimes of considerable volume, is not uncommon in myxedematous patients and may be mistaken for enlargement of the heart. It, too, disappears under adequate replacement therapy.

The function of the heart and circulation in clinical myxedema is indolent; the cardiac output is diminished, the circulation time prolonged, and plasma and blood volumes are usually reduced.

Ellis and coworkers21 have lately reported results of detailed hemodynamic studies in five myxedematous patients. In three, though the heart was enlarged, the pressure gradients in the central veins, right auricle and ventricle and pulmonary artery were normal. There was no clinical evidence of heart failure; cardiac output was reduced to a degree equivalent to the basal metabolism. In another case, although dyspnea, orthopnea and peripheral edema suggested myocardial insufficiency, and cardiac output was reduced out of proportion to the lowered metabolic rate, there were no measurable signs of stasis in the pulmonary circulation, heart or systemic veins at rest or with moderate exercise. Upon thyroid therapy blood flow and oxygen consumption returned to normal. In the fifth, an older patient who had had increasing dyspnea on exertion, cardiac output was also markedly reduced. Pulmonary arterial pressure and diastolic pressure in the right ventricle rose with exercise, a common accompaniment of myocardial failure. Angina pectoris on effort, inverted T waves in all leads and a prolonged QRS interval indicated that in this case coronary insufficiency and myxedema...
combined to produce disability. Dyspnea abated under treatment with thyroid, but angina persisted in some degree tending to be worse with larger doses of the drug.

These carefully studied patients are representative of the variety of circulatory responses to the myxedematous state in man. Inasmuch as myxedema is predominantly a disease of middle age or after, there is a significant probability of other concurrent conditions which would decrease cardiac reserve, notably degenerative vascular disease. And yet, although the state of the heart and circulation may differ profoundly from the normal, true myocardial insufficiency is detectable only in a minority of instances in which blood flow is depressed out of proportion to the body's oxygen demands. In any event, digitalis rarely restores circulatory efficiency in these cases. The beneficial effect of thyroid therapy upon the circulatory apparatus is more likely to accomplish this even though the demands for blood flow are increased at the same time by the general metabolic effects of the hormone.

Angina pectoris as a complication of untreated myxedema has evidently occurred infrequently. Willius and Haines in a series of 162 cases of severe myxedema observed only one patient with angina. Smyth collected 578 cases from the literature among which angina had been described in only five instances, and added one more.

The occurrence of coronary insufficiency with cardiac pain in treated cases of hypothyroidism is rather more complex. In some patients with myxedema, angina appears during thyroid therapy, and doses which are tolerable to the heart in these cases may fail adequately to relieve the symptoms of hypothyroidism. In others, angina occurring during the myxedematous state is relieved following the administration of thyroid. Evidently, here as with congestive failure, the result depends upon the balance between improvement in the status of the myocardial blood flow on the one hand, and the increased cardiac work demanded by the general metabolic effects of the thyroid therapy. This should, therefore, be administered with caution, commencing with small (8 mg.) daily doses. Fatal instances of myocardial infarction during thyroid therapy of myxedema have been recorded.

The striking and often lasting relief of congestive cardiac failure or of the symptoms of coronary insufficiency in patients with hyperthyroidism when the thyrotoxicosis is reduced has led to the trial of induced hypothyroidism in the therapy of intractable heart disease or angina pectoris in euthyroid patients. Prior to the development of drugs capable of suppressing the activity of the normal thyroid, resort was had to total thyroidectomy for this purpose. The effects of this procedure in 362 patients were reported in 1937. Operative mortality was 10 per cent among those with congestive failure and 5 per cent in those with angina pectoris. Sixty-four per cent of 229 patients with congestive heart failure were considerably improved, some dramatically so. In 56 per cent of 133 patients with angina pectoris, the results were excellent; in an additional 28 per cent benefit was moderate only. In the remaining patients in both groups little, if any, improvement was accomplished. In another series 13 of 15 patients subjected to subtotal thyroidectomy showed complete disappearance or marked improvement of angina pectoris for periods ranging from 8 months to 17 years.

Following the application of thiouracil derivatives to the treatment of thyrotoxicosis and the demonstration that the activity of the normal thyroid could be considerably depressed thereby, total thyroidectomy has been largely abandoned in favor of medical measures for inducing hypothyroidism in patients incapacitated with heart disease. With doses of 0.3 Gm. to 0.6 Gm. of thiouracil daily some benefit can be conferred in a majority of patients with severe angina pectoris or advanced cardiac failure. Improvement, when it comes, is not to be expected within a month or often more after beginning treatment. Symptomatic response usually corresponds to the degree and constancy of lowered metabolism, although in some reported instances improvement is described without evident hypothyroidism. Though thiouracil therapy has the advantage of producing a reversible inactivation of the thyroid gland,
Enthusiasm for this method of therapy is tempered in some quarters by concern that hypothyroidism, whether spontaneous or induced, may critically accelerate the development of atherosclerosis in systemic, or particularly in the coronary, arteries. Space does not permit a full analysis of this problem which would involve detailed review of current concepts of the biology of atherosclerosis, but it is pertinent to examine the principal sources of this concern.

Soon after the recognition of the basic connection between cretinism and hypothyroidism toward the end of the last century, it was demonstrated that total removal of the thyroid in young animals (sheep, goats and rabbits) was followed by extensive arteriosclerosis of large arteries. These observations have been repeatedly confirmed though at least one investigator, Goldberg, has been at pains to point out essential histologic differences between some of the arterial changes so produced and atherosclerosis in man.

The modern interest in the role of cholesterol in atherogenesis has focused attention upon a possibly controlling influence of the thyroid upon this process. It has been shown that rabbits can be protected from the development of atherosclerotic lesions following cholesterol feeding by the simultaneous feeding of desiccated thyroid. Recently it has been demonstrated that suppression of thyroid activity with thiouracil augments the extent and severity of atherosclerosis developing in dogs fed relatively large quantities of cholesterol. Thiouracil feeding alone, even when continued for 15 months, although it may be accompanied by an increase of several fold in the blood cholesterol in these animals, does not cause arterial disease. The role of hypothyroidism in this process appears to concern the disposal of cholesterol. Dogs can normally metabolize large quantities of this material after ingestion without accumulating high levels of cholesterol in the blood. When, however, thyroid function is suppressed by thiouracil, the ingestion of such amounts of cholesterol results in fantastically high blood levels and the arterial lesions which then

in a significant proportion of cases it may suddenly provoke fever, granulocytopenia, or agranulocytosis. When such manifestations appear, thiouracil must, of course, be discontinued. On the other hand, some patients tolerate the drug well and in some of the reported cases it has been administered for three years or longer.

Radioactive iodine (I\textsuperscript{131}) which has become available from the atomic pile has recently been applied to this same purpose. While the avidity of the normal thyroid for I\textsuperscript{131} is less than that of the overactive gland in the patient with thyrotoxicosis, persistent hypothyroidism can regularly be induced in euthyroid patients without deterrent toxic effects, though more than half show transient signs of thyroiditis with mild elevation of basal metabolic rate within the first two to four weeks after treatment, occasionally accompanied by temporary increase in frequency of anginal attacks. In some, notably those with thyroid adenoma, repeated doses of I\textsuperscript{131} are required before persistently lowered metabolic rate is induced. Clinical improvement corresponds closely in time and degree with the clinical and laboratory signs of hypothyroidism, although benefit does not evidently depend upon lowering metabolism to the level of true myxedema. When this is accomplished the attacks of pain become milder, or occur only on greater effort, or orthopnea or dyspnea diminish. Blumgart, whose experience with this therapy has been long and extensive, recommends that after genuine signs of hypothyroidism have appeared, thyroid be administered in doses just sufficient to maintain metabolic rate at a level of −20 to −25 per cent. Usually this requires 6 to 30 mg. per day.

Upon this regime, excellent results are obtained in about 40 per cent of cases and considerable benefit in an additional 20 per cent. Like other methods of inducing hypothyroidism, this treatment should be reserved for the severely incapacitated patients and then applied as an adjunct to other appropriate therapy. It is unlikely to be beneficial in the presence of disease causing progressive deterioration of cardiac function, such as malignant hypertension or rheumatic carditis.
develop seem to be related quantitatively to this degree of hypercholesterolemia.

Although the literature contains some very dogmatic statements to the effect that myxedema and coronary artery disease are frequently if not invariably associated, there are few reported instances of untreated myxedema in man in which the arterial system has been carefully and completely examined. In the report of the Committee of the Clinical Society of London to Investigate the Subject of Myxedema, the state of the arteries was mentioned in 84 cases; they were described as "atheromatous" in five. The report concludes that myxedema provokes no unusual degree of arterial degeneration. More recently a few instances of long-standing, fatal myxedema or diminished thyroid function in aged persons, cystic degeneration of the medial muscular coat of the aorta, sometimes with rupture, has been described. Certain other reports are impressive in presenting the picture of precocious atherosclerosis in relatively young myxedematous patients. In still others the majority of patients described were at middle age and beyond, a period when coronary artery disease is more common in euthyroid persons.

One implication does emerge from the literature dealing with atherosclerosis and myxedema which may have special significance. Bartels and Bell, reporting 15 instances of coronary artery disease among 59 cases of spontaneous myxedema, found that in the women under 50 in this series coronary disease was no less common than in men. The usual ratio at this age is four cases in males to one in females. Though derived from a small number of cases the observation of Bartels and Bell possibly indicates that myxedema may diminish the sex-determined difference in the incidence of coronary artery disease in middle life.

On the other hand Blumgart, Freedberg and Kurland, describing the state of the arteries in eight patients rendered hypothyroid for therapeutic purposes, report no significant differences in comparison with euthyroid patients despite lowered metabolism for 1 to 13 (average 7.4) years. The blood cholesterol in these patients had been persistently elevated and, as recently demonstrated, the lipoprotein molecules associated by Gofman with atherogenesis were measurably increased.

In summary, atherosclerosis can be produced, or its development accelerated in animals by surgical ablation of the thyroid at an early age or by the combined effects of chemical suppression of thyroid function and the ingestion of abnormal quantities of cholesterol. Opportunities for definitive studies of the vascular system in unrelied cases of human hypothyroidism seem to this writer to have been too few to provide conclusive evidence that augmented atherosclerosis is an inevitable consequence. Without minimizing the contribution of animal experimentation to our knowledge of arterial disease, the gap between the human disease and cholesterol-induced atherosclerosis in hypothyroid or athyroid animals cannot be said as yet to have been fully bridged in all details. The athyroid state is a complex of reactive changes in several endocrine functions. The suggestive finding that myxedema may affect adversely the relatively lower incidence of atherosclerosis in the female suggests a secondary gonadal influence.

In any event, the weight of evidence indicates that the benefit conferred by induced hypothyroidism in selected cases of coronary insufficiency or myocardial failure is too real to be ignored. At the same time, it is desirable to produce the minimal suppression of thyroid function which will accomplish relief of the cardiac symptoms. It is, moreover, essential that no chance be overlooked to follow carefully cases so treated with reference to the development or progress of signs and symptoms of vascular disease intra vitam, and to conduct detailed comparison especially of the coronary vessels with those of euthyroid pa-
tients post mortem. For the present it seems wise to view the procedure on the one hand as a calculated risk and on the other as a special challenge to a more complete and fruitful understanding of the pathogenesis of atherosclerosis.

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