Thyroid Function and its Possible Role in Vascular Degeneration

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Publication Number 108

AMERICAN LECTURE SERIES

A Monograph in

AMERICAN LECTURES IN CIRCULATION

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Preface

THE OBJECTIVE of this paper is to call attention to the relative role of thyroid function and nutrition in vascular degeneration.

It is becoming more and more evident that the thyroid gland through its influence on nutrition may be an important factor in body degeneration. The etiological factors of arteriosclerosis have long been attributed to different mechanisms. Too little attention has been paid to the internal metabolism and blood supply of the blood vessel walls as a cause of arterial degeneration.

In this paper observations are reported correlating the post mortem findings of arteriosclerosis with the clinical state of the individual before death. Evidence of hypothyroidism and advanced arteriosclerosis was exceedingly common in these studies. Even age was not so important a factor as was evidence of decrease in oxygen consumption. Clinical observations were made on individuals with low metabolism by administration of thyroid with an attempt to maintain a normal basal metabolic rate. Controls were used and it was found that the administration of thyroid was accompanied by a decrease in incidence of certain manifestations of arteriosclerosis. The necessity of treating arteriosclerosis by proper regulation of the rate of oxygen consumption even at an early age is important.

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ORIENTATION

THE CONSIDERATION of the relationship of the activity of the thyroid gland to the development of arterial degeneration makes it imperative that we review some of the facts that are known about the two conditions. It is of importance that we assess any observations that may link these two states together. It is known that hypothyroidism as manifest by the low basal metabolic rate is frequently associated with arteriosclerosis. It is also known that increased lipid content of the blood is frequently associated with hypothyroidism and has been considered a factor in the production of arterial degeneration. It is well known that arteriosclerosis occurs chiefly in older people and it has been shown that decreased thyroid function generally occurs in the aged. It has likewise been shown that degeneration of the blood vessel walls may occur in cretinism, myxedema, and in total thyroidectomy. We shall, therefore, attempt through our own observations and those of others described in the literature to establish a relationship of the two conditions.

In order to present a clear picture of my conception of the clinical and anatomical aspects of the

problem I should like to review two cases that have come under my observation, one of which has been recently reported.[43] Both of the individuals were carefully worked up clinically, and, after death, anatomically. They were approximately the same age at time of death. One of the individuals had had his thyroid removed five years before death. The other, as far as could be ascertained, had a normally functioning thyroid gland but a disturbed lipid metabolism.

The first case is that of H. H. who in 1935 entered Barnes Hospital at the age of 49. His diagnosis at that time was advanced pulmonary emphysema, the etiology of which was thought to be associated with influenza in 1918. His vital capacity was 1700 cc. An x-ray showed emphysema of the lungs but no arteriosclerosis of the pulmonary artery or the aorta was recognizable. His basal metabolism upon admission into Barnes Hospital was found to be plus 12 with a blood cholesterol of 180. Because of the extreme difficulty in breathing an attempt was made to reduce his oxygen need by means of thyroidectomy. He was operated upon and a total thyroidectomy was performed. He was then followed in the clinic and continued to be observed until his death approximately five years later. Three months after the operation the basal metabolism was found to be minus 24 and the blood cholesterol was 200. During the period after the operation he had been given iodine in a cough mixture as an expectorant. The patient did not show any marked improvement of his clinical state following his operation. Dessi-

cated thyroid in small doses was offered from time to time but the patient felt that the substance made him worse clinically and he took very little of it. He, however, was forced to lead a sheltered and protected life because of his asthmatic type of breathing and he continued to live for a period of five years. At the end of his fourth year his basal metabolic rate was minus 30 and his blood cholesterol 210. A notable change from the previous x-ray of the chest was evidence of calcium in the aorta as well as increased tortuosity of the vessel which was not seen in the initial x-ray. The patient died of coronary thrombosis on September 16, 1940.

The following is the statement of the prosector of the autopsy: "For a man, age 54, the aorta is remarkable for its extreme degree of arteriosclerosis. Beginning at the arch and proceeding down to the abdominal aorta there is an unusual amount of plaquing of the intima. There is practically none of the intimal coat uninvolved. Some plaques are entirely calcified while others are ulcerated." In some areas the intima is replaced by a blood clot at various stages of organization. The aorta is without any degree of elasticity. No thyroid could be found at autopsy. Microscopically, the aorta shows an advanced calcification of the intima which extends well into the media. The elastic tissue is not seen, even with special stain. Some small elastic fibriles are observed which appear to be frayed and broken. In some areas of the media, chiefly in the external layer, there could be seen an abnormal acidophilic substance between the muscle bundles. The media

showed a general disorganization of the bundles and much of it consisted of an amorphous substance. The heart was somewhat enlarged, and the coronaries were sclerotic. The right coronary artery was occluded 1 cm. from its orifice, this process being precipitated by marked roughening and calcification of the intima. There was a tear in the coronary at this site.

This individual had had his thyroid removed in an attempt to relieve the burden of oxygen need in emphysema. He lived for five years without his thyroid gland. At his death at the age of 54 due to a coronary thrombosis and splitting of the coronary artery, advanced arteriosclerotic changes were noted in the aorta and its immediate branches. The degree of arteriosclerosis appeared to be much greater than is common even in individuals much older than this patient.

The second patient, a female age 54, was first seen on 5/6/46 and gave a history of an attack of coronary thrombosis a year and a half before. She had been found to have some elevation of the blood pressure on previous examinations. Her blood cholesterol level when first seen by me was 651 and her basal metabolic rate was plus 1. There were no signs of disturbed thyroid function. She was admitted to Barnes Hospital on 2/8/47 for study because of a precordial pain. At that time she had a basal metabolic rate of plus 4 and 0 and a blood cholesterol of 500. The diagnosis of myocardial disease and hypercholesterolemia was made. An x-ray study showed no calcium in the blood vessels.

The patient died suddenly on 2/27/47 while playing bridge. An autopsy was performed on the patient and the essential findings were as follows: The heart was of normal size. The anterior descending branch of the left coronary artery was thrombosed and the coronary arteries showed considerable atheromatous material along the intimal surface. An ulceration of the atheromata was noted in the left coronary artery with a thrombus extending into the anterior descending branch. There was a scar at the apex of the heart and some adhesions were attached to the precordium over the area. The heart muscle otherwise appeared to be normal, except for the area supplied by the thrombosed vessels, which appeared pale. The aorta showed a moderate number of plaques with atheromatous material throughout its entire length. The plaques were most extensive in the ascending and the abdominal portion of the vessel, although occasional ones were seen in other areas. The intima of the aorta had a normal appearance except over the plaques. The renal blood vessels as well as the iliac arteries showed considerable atheromatous deposits in the intima. The aorta was elastic. Microscopical sections of the aorta and coronary arteries revealed deposits of atheromatous material, containing cholesterol crystals. The media appeared normal and the elastic tissue element was quite prominent. The only degenerative changes noted in the media were hyalinization of the muscle fibers immediately proximal to the atheromatous accumulation of the intimal surface. The thyroid gland was normal.

The anatomical findings in these two individuals

revealed that both died of coronary thrombosis associated with arterial degeneration, and the anatomical changes that led up to the deaths were as varied as their clinical backgrounds. It has been noted that both were of the same age at death. One was a male, the other a female. The male patient had no thyroid at the time of autopsy. He revealed an advanced arteriosclerosis which was much more advanced than we had ever seen in any other individual at the age of 54. The autopsy revealed that the nature of his arteriosclerosis was of such an extent that it involved the entire wall of his aorta and larger blood vessels. The muscle layer showed an advanced degenerative change with calcium deposits, hemorrhage, and degeneration. The intimal layer was likewise involved with atheromatous material and calcium deposits. The elastic tissue of his larger vessels was difficult to distinguish even though elastic tissue stains were used. The vasa vasorum was seen, but the vessels appeared small and in some slides, occluded. This individual presented a picture of degeneration of the entire vessel wall.

The other individual, the woman whose thyroid was found to be intact at autopsy, and the morphology of whose gland appeared to be normal, gave an entirely different impression of the blood vessels. The intimal layer of the vessels, particularly the coronary artery and aorta, showed considerable infiltration of atheromatous material containing cholesterol crystals. Grossly, the aorta remained elastic. Some degeneration of the smooth muscle in the media was noted but this occurred directly beneath the areas of

atheromatous material seen upon the intimal surface. In no instance did the atheromatous material extend deep into the muscle and one did not see diffuse degenerative changes of the muscle bundles. In addition to the different intimal pictures, the pathological study revealed that the coronary thrombosis occurred as a result of different mechanisms. In the male, the athyroid individual, the wall of the coronary blood vessel was broken, and there was a rather large hemorrhage into the wall which pushed the intimal surface forward and caused it to occlude the vessel lumen. In the female with high blood cholesterol there were atheromata in the coronary artery with ulceration, the thrombus of which had formed as a result of a breaking off of a plaque and occlusion of the coronary artery. A further comparative point in the two individuals was that in the athyroid individual calcium deposits were seen both in the media and in the intima of the aorta and coronary arteries, while in the individual with the normal appearing thyroid the lesions were all near the intimal surface. It is of interest, too, that the athyroid individual never revealed a blood cholesterol that could be considered high. The maximum blood cholesterol level obtained was around 266. This may well have been due to the fact that he did not eat a great deal because of his asthmatic state and that there was a gradual decline in his nutrition.

According to our interpretation of the clinical and anatomical factors presented by these two individuals, arterial degeneration may occur both in individuals with a normal thyroid activity with in-

creased blood cholesterol levels and in individuals who have had their thyroid function reduced. There is a characteristic difference, however, in the two. The degenerative change that occurs in individuals with hypothyroidism would seem to be primarily medial, whereas in individuals with high lipid content of the blood the degeneration may be chiefly intimal. These two individuals demonstrate clearly that arterial degeneration is not due to any one single factor. Different factors appear to enter and produce different forms of disease which we shall discuss later. Since the cause of general degenerative changes of the blood vessels, known as arteriosclerosis, must undoubtedly be due to different etiological agents, even though evidence from the preceding data indicates that the reduced function of the thyroid gland would appear to be an important factor, the question of just how this gland may bring about its part in the change to arterial sclerosis is important but somewhat speculative. To properly evaluate the early disease process that occurs in the arteries in hypothyroidism it is important that we review the activity of the thyroid gland as far as its influence on the vascular system is concerned and also review some of the conditions that have been suggested as a cause of arterial degeneration.

THYROID ACTIVITY IN RELATION TO ARTERIOSCLEROSIS

The activity of the thyroid gland, as far as its influence on the blood vessels is concerned, may be

divided into a primary and a secondary function. Its primary function would seem to be its activity as a metabolic stimulus to body tissue, including the vascular system, whereas the secondary function is a resultant of the metabolic stimulus and is manifest more directly on functional activity of irritable tissue. As far as the primary function of the thyroid is concerned we all know that it is a member of the complex hormonal system of the body and its primary function is coordinated with the other glands of internal secretion. The hormone produced by the thyroid gland was first isolated by Kendall in 1918 and is known as thyroxine. The substance has a general effect on the metabolism of the organism, particularly on the burning of carbohydrate, protein and fat.

It has been shown in an animal after thyroidectomy that there is a decreased excretion of nitrogen, whereas after administration of the thyroid hormone there is a great increase in the nitrogen output. The increased nitrogen metabolism is believed to express the breakdown of protein. Many experiments may be cited which indicate that the thyroid plays an important role in protein utilization by the body. The influence on carbohydrate utilization in the body may be shown by the studies on the blood sugar. Animals or individuals fed thyroid are frequently seen to have hyperglycemia and occasionally glycosuria. It has been noted further that the total abolition of the thyroid gland increases sugar tolerance roughly parallel to the decrease of the metabolic rate. Information with regard to the influence of the thyroid

hormone on fat metabolism is like the knowledge of fat metabolism in general, very meager. It is known, however, that a high percentage, as much as seventy per cent of subcutaneous and muscle fat may be lost on thyroid feeding. Prolonged administration of thyroid usually results in a drop of lipid content of the blood, whereas a rise is noted after thyroidectomy. Evidence has accumulated to indicate that elderly individuals who commonly have arteriosclerosis may have a disturbance of metabolism of either one or all of these food substances.

Aside from the effect on the metabolism of the three types of foods, another possible effect that thyroid disease could have is upon water metabolism. The thyroid hormone has an influence particularly on water and salt metabolism of tissue cells. It has been shown that injection of thyroxine in normal animals produces hydremia with a water and salt diuresis. It is believed that this water is primarily from the body cells because of the relatively high content of potassium salts found in the urine. Under conditions of prolonged abnormal thyroid activity changes in the electrolytic content of the blood occur which disturb the acid base equilibrium which is likely to bear towards the acid side with a simultaneous increase in blood calcium. Continuous administration or production of the thyroid hormone produces a negative calcium balance together with a loss of magnesium and other inorganic constituents of the body. The converse is also true since hypothyroidism may also produce a state of negative calcium balance. It can be seen that the primary effect of thyroid func-