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On the Genesis of Atherosclerosis*

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ABSTRACT: **Although atherosclerosis has been known for over 3000 years, it came into prominence in the 20th century apparently because a reduction in deaths from infections permitted a population susceptible to atherosclerosis to reach adult life. Atherosclerosis is accompanied by an early deposit of abnormal quantities of mucopolysaccharides in the tissues. In hypothyroid children, the tissue content of mucopolysaccharides is increased, but is restored to normal by thyroid therapy. A factor in the increased death rate from atherosclerosis seems to be the survival of hypothyroid children from infectious diseases; they thus become potential candidates for premature death from atherosclerotic disease. Thyroid therapy can be a prophylactic agent against premature deaths from heart attacks, hypertension, and diabetes.**

New catastrophes arise to plague the human race as rapidly as the old ones are eliminated. Two hundred years ago it was smallpox, but immunizations permitted the babies to live longer and, tuberculosis took over as "Captain of Death" one hundred years ago. Today it is atherosclerosis, and there is reason to believe that it will still be the same one hundred years hence.

A natural sequence of events led to the rise of tuberculosis; babies survived to a new age group. Also a natural sequence of events led to the rise of heart attacks. Tuberculosis kills at an average age of less than 40 years, whereas for heart attacks 65 years is the average. Modern autopsy studies offer convincing evidence that premature deaths from atherosclerosis are occurring in the escapees from deaths by infectious diseases.

Atherosclerosis is not a modern invention; it was present in the Egyptian mummies entombed over 3000 years ago. Its phenomenal rise in the 20th century is again a natural consequence of the reduction in early deaths from infectious diseases. The antibiotic drugs have been a much more potent factor in the rise of heart attacks than all of the other changes in diet or living habits combined. Longer survival has allowed a natural process of aging to continue.

There is little hope of abolishing atherosclerosis; to do so would be the equivalent of discovering perpetual motion. No worse catastrophe could occur. However, concrete evidence is accumulating that we can prevent many of the premature arterial degenerations and allow most persons to attain their "three score years and ten." Why did Parrish (1) observe that, at autopsy, no coronary sclerosis can be found in 8 per cent of males over 70 years of age, yet 27 per cent of fatal heart attacks occur before the age of 65? Obviously there is a difference in susceptibility, and that difference deserves the closest scrutiny.

THYROID DEFICIENCY AND ATHEROSCLEROSIS

The answer was found in the routine autopsies at Graz, Austria, where about 75 per cent of the persons who die in this city of 230,000 are examined post mortem in the largest pathology institute in the world. The protocols from over 70,000 autopsies covering the period 1930-1972 have been personally reviewed (2). This is a goiter region, and the entire population suffers from some degree of hypothyroidism. Iodized salt was not introduced until 1963, at which time goiters were the rule.

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Graz was chosen as a study area in order to see the influence of thyroid deficiency on atherosclerosis. The autopsies revealed that there is more coronary sclerosis in Graz than in the United States. Arterial damage begins at an earlier age and progresses faster; by age 70 it is hard to find either a male or a female without far-advanced coronary damage. But a paradox appears; Graz has a low incidence of myocardial infarction.

In 1930 the incidence of fatal coronary disease was no greater in the autopsies at Graz than in those among the Bantu of South Africa. Yet Graz is a city with a long history of industrialization, modern medical techniques, and a diet quite similar to that eaten in America. Another "fly in the ointment" appeared. A review of the autopsies carried out during World War II revealed that although heart attacks dropped 75 per cent during the war, coronary atherosclerosis increased fourfold. About twice as many persons showed coronary damage, and the degree of involvement was about twice as great in each case.

Three facts stood out very clearly from this huge number of autopsies: 1) A change in diet did not account for the drop in heart attacks during the war. 2) Thyroid deficiency is a powerful atherogenic agent. 3) The inhabitants of Graz did not show a high incidence of heart attacks, as in other modernized communities.

INFECTIONS, ATHEROSCLEROSIS AND HYPOTHYROIDISM

Although heart attacks were rare in Graz in 1939, the incidence fell an additional 75 per cent by 1944. This drop was comparable to that seen in other European countries during the war. The same reduction in dietary saturated fats took place in Graz as elsewhere. The fourfold increase in coronary sclerosis occurred despite a frugal diet. Some unknown factor had lowered the coronary death rate against a rising coronary sclerosis rate. The answer was simple when the various categories of death for 1939 and 1944 were compared. The war had caused a tremendous rise in deaths from tuberculosis and other infectious diseases. These had removed persons afflicted with accelerating coronary sclerosis, before myocardial infarction could occur.

Each country in Europe which showed a drop in heart attacks during the war showed a marked rise in infectious deaths, including tuberculosis. This is a far more powerful deterrent to coronary occlusion than the alleged influence of diet. At Graz the number of extra deaths from tuberculosis alone was threefold greater than the drop in heart attacks. The autopsies revealed that these premature deaths from infection indicated accelerated atherosclerosis. The circumstantial evidence that diet accounted for the decrease in coronary disease during the war must give way to cold facts obtained at the autopsy table.

It is apparent from the autopsy studies that the prevalence of infectious diseases at Graz was related to the low incidence of heart attacks before the war and the further decrease during the war. In each of the underpriviledged countries, infectious diseases are rife and could account for the scarcity of heart attacks. This can be illustrated by the Bantu, who had a death rate from tuberculosis in 1954 equal to that in the United States one hundred years ago. No deaths from myocardial infarction were recorded in our country or elsewhere in 1873; the term had not been coined at that time.

The autopsy protocols were sought in 1958 because twenty years of personal experience had indicated a very low incidence of heart attacks in thyroid-treated patients. Experimental evidence had indicated that thyroid deficiency enhanced atherosclerosis and thyroid administration delayed it in animals (2). The autopsies at Graz demonstrated that the human behaved as did other animals.

These and other observations throughout the world force a new interpretation of the genesis of atherosclerosis. There have always been many inconsistencies in the diet and environmental theories. Evidence for the thyroid-deficiency theory began in 1877 with an autopsy by Ord (3) on a 58-year-old female with a peculiar edema that did not weep when the surface was cut. She had advanced generalized atherosclerosis long before modern environmental factors entered the picture. Chemical analysis of the connective tissues revealed mucinous, glue-like substances which had a great affinity for water. Ord named the disease "myxedema."

Information on the mucinous substances, now called mucopolysaccharides, has been updated by modern chemical studies. These

compounds are known to accumulate early in any trauma or inflammation, or in atherosclerosis. Asboe-Hansen (4) confirmed the high tissue concentration of this material in adult hypothyroidism; furthermore, thyroid therapy returned the concentration to normal. Andersen et al. (5). in a study of athyreotic children, found a normal tissue content of mucopolysaccharides in the euthyroid state, a rapid rise within six weeks after omission of thyroid therapy, and a prompt fall to normal levels with the resumption of thyroid therapy. Clearly the thyroid hormone is important in the control of the mucopolysaccharides.

The next milestone was the autopsy demonstration by Zinserling (6) in 1925 of atherosclerosis in babies 6 months of age. By the age of 4 years, most such children showed arterial damage. Again environmental factors such as lack of exercise, smoking, and an abnormal diet could not be at fault. However, one contributing factor was present, namely, a susceptibility to infectious diseases. Most deaths among babies are due to infections. Zinserling believed that infections did not cause the atherosclerosis but were accompanied by it. His point is well taken.

Certainly an acute infection might cause death within a matter of hours, but the appearance of atherosclerosis would take considerably longer. It seems more reasonable to assume that the fatal infection developed in a child with a progressing atherosclerosis. At the present time the only disorder known to be associated with a rapid, spontaneous deposition of mucopolysaccharides in children is hypothyroidism. Not only are hypothyroid children susceptible to atherosclerosis, but they are also highly susceptible to infectious diseases. This has been the missing link in the genesis of atherosclerosis.

Now it is clear why heart attacks were rare throughout the world as long as infectious diseases dominated the medical scene; the most susceptible individuals died before coronary occlusion could occur. In the countries that are developing modern health measures, deaths from infections have declined rapidly during the 20th century, and deaths from atherosclerosis have shown a prcportionate rise. Graz, Austria, was an exception. Despite modernization, a drop in infections did not occur until antibiotic drugs became available. Infarctions are now climbing rapidly, and the rise is reciprocal to the infections.

Autopsy studies on Bantu children and young adults have revealed more arterial damage than is present in similar age groups in our own country, yet the incidence of coronary disease has been very low in the Bantu. Now the paradox disappears; premature deaths from infections have been eliminating the candidates for early infarctions. Recent reports indicate that deaths from tuberculosis are declining rapidly in South Africa, and premature coronary deaths are mounting.

Although the autopsies carried out during the war at Graz indicate that our problem of atherosclerosis might be abolished within five years by bringing back tuberculosis, the associated morbidity and shorter life span do not sound enticing. The results of the present study indicate that the rate of premature deaths from coronary disease might be influenced by simply selecting patients with hypothyroidism and treating them with therapeutic doses of thyroid hormone.

Our problem is to recognize the thyroid deficiency. Symptoms alone can be the basis for the diagnosis. It must be remembered that the thyroid affects every cell in the body. Location of the symptoms may vary from the skin to the respiratory system, the nervous system, the digestive organs, and even the reproductive organs. The chemical tests for thyroid function are of little help; the results are often inconsistent and only add to the confusion.

Basal temperature has been found a satisfactory test for over thirty years. If the axillary temperature is below 97.8° F before arising in the morning, the patient usually will tolerate thyroid therapy. Oral temperatures are often misleading due to the presence of postnasal drip. Few cases of hypothyroidism will be missed if basal temperatures are routinely recorded for patients not responding to the usual medications.

THYROID THERAPY

Thyroid dosages should be low initially and increased at monthly intervals. However, the basal temperature should never become elevated above 98.2° F. Table 1 illustrates the results of such a program carried out for over thirty years.

The Framingham Report in 1957 established the incidence of new coronary disease in a fixed population examined periodically. Since

TABLE 1
The Rarity of New Cases of Coronary Disease in Thyroid-Treated Patients

Sex	Condition	No. of Patients Treated	Patient-Years	No. of Cases of Coronary Disease Expected*	No. of Cases of Coronary Disease Observed
F	Age group, 30-59	490	2705	7.6	0
F	High-risk†	172	1086	7.3	0
F	Age over 60	182	955	7.8	0
M	Age group, 30-59	382	2192	12.8	1
M	High-risk†	186	1070	18.5	2
M	Age over 60	157	816	18.0	1
Totals		1569	8824	72.0	4

* Compared with the Framingham study.
† Hypertension and/or hypercholesterolemia.

the examinations and the intervals corresponded very closely to those in the present study, the two groups can be compared. The last line in Table 1 summarizes the results on 1569 cases studied over 8824 patient-years. Only 4 new cases of coronary disease were observed in the thyroid-treated group although 72 might have been expected from matching the groups according to age, sex, hypertension, and presence of hypercholesterolemia. The results indicate protection from premature coronary disease in 94 per cent of the cases.

The only change in these 1569 cases was the relief of thyroid deficiency. There were no changes in diet; smoking was not curtailed; exercise was not encouraged; nor were other modes of living altered. Further evidence that the thyroid therapy was efficacious was supplied by 30 "dropouts" in whom fatal myocardial infarctions developed within six years after stopping thyroid therapy. Most of these patients were in the younger age group; one was only 23 years old.

If premature heart attacks occur in hypothyroid patients, hypothyroidism must have risen rapidly during the 20th century. Susceptibility to infectious diseases is a cardinal sign of hypothyroidism. Each escapee from an infectious death is a potential candidate for early myocardial infarction.

If the deposition of mucopolysaccharides is important in atherosclerosis, and if hypothyroidism favors such deposition, it is possible that some degree of hypothyroidism is present in other degernerative diseases accompanied by atherosclerosis. Personal experience indicates that this may be true to two diseases in which arterial damage is extensive — hypertension and diabetes. For twenty years Menof (7) in South Africa has insisted that many cases of hypertension respond to thyroid therapy alone. Among the 1569 patients in the present study, 127 had hypertension at the start of observations. In 102, or 80 per cent, the blood pressure returned to normal without any other medication. In 19 others there was no increase in the blood pressure which was mildly elevated and required no other ttherapy. Only 6 cases showed a progressive rise necessitating specific treatment for hypertension.

Many patients with hypertension have symptoms common to hypothyroidism, including a subnormal basal temperature and a reduction in the velocity of conduction along the peripheral nerves. It is no surprise that all of these findings respond favorably to thyroid therapy; the drop in blood pressure is only a fringe benefit for the improvement in health.

In the diabetic patient, arterial damage appears earlier and progresses faster than in the general population. Pathologists have been unable to demonstrate any other difference between the atherosclerosis of the diabetic and that of the nondiabetic patient. Among the diabetic patients in the present study, complications were conspicuous by their absence. In twenty years no blindness, kidney failure, gangrene or neuropathy had occurred. Each of these atherosclerotic disorders is characterized by a marked increase in local deposits of mucopolysaccharides.

Thyroid therapy had been started in the diabetic patients of present study in an attempt to lower the serum cholesterol level. When evidence appeared that it also lowered the high mucopolysaccharide content of the tissues, this seemed a rational explanation for the absence of complications in these thyroid-treated pa-

tients. Our results suggest that the atherogenesis in diabetes is not due to the disturbance in carbohydrate metabolism but to an associated hypothyroidism.

This independent contribution to medicine turned out to be only confirmation of a neglected report by Dr. C. D. Eaton (8) of Detroit in 1954. Only a year ago his paper was rediscovered. He had spent many years treating hundreds of diabetic patients. He found that hypothyroidism was more prevalent than in the general population and that thyroid therapy prevented the vascular complications of diabetes. If the diabetologists had heeded his contribution, perhaps thousands of diabetic patients might have been spared morbidity and premature deaths.

In a few cases of diabetes, vascular complications never develop regardless of the severity or duration of the disease. No studies are available, but the thyroidal status of such patients should be of interest. It would be no surprise if their basal temperatures were in the upper limit of the normal range or slightly elevated.

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