RANDOM THOUGHTS ON CORONARY ARTERY DISEASE

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Before the year 1912 the concept of myocardial infarction as being caused by obstruction of the coronary artery was not recognized. The histopathology of infarction was well known but no attention was paid to its relationship with disease of the coronary arteries. In the latter part of the sixteenth century William Harvey found at autopsy rupture of the wall of the left ventricle. This observation passed unnoticed for 4 centuries. In the latter part of the nineteenth century Weigert in 1880, Conheim in 1861, and Huber in 1882 demonstrated in scientific articles published in Virchow's Archives, the foremost journal of research at the time, the relationship between coronary occlusion and myocardial infarction and fibrosis. Despite this, such distinguished contemporary clinicians and scientists as Laennec (1781-1826) in Paris, Virchow (1821-1902) in Berlin, and Rokitansky (1804-1878) in Vienna failed to recognize myocardial infarction and considered myocardial fibrosis and aneurysmal bulgings as merely a result of some inflammatory process and acute infarcts as fatty degeneration of the myocardium. Verily, Goethe spoke the truth when he said, "Was man weiss, sieth man." (What one knows, one sees.) None of those outstanding clinicians and pathologists saw the relationship between coronary obstruction and myocardial infarction because they failed to know its existence, and so the medical profession at large neglected to take notice of a condition that is so well known today by even the ordinary man in the street. The consciousness of the medical profession regarding the existence of a tie-up between coronary occlusion and myocardial infarction was aroused in 1912 by the publication of the epoch making paper of James B. Herrick of Chicago entitled "The Clinical Features of Sudden Obstruction of the Coronary Arteries."

Herric pointed out that coronary obstruction was a frequent cause of death and gave the medical profession the earliest complete clinical description of sudden coronary occlusion. His pupil, Fred Smith, in an experimental study of sudden coronary occlusion described certain changes in the electrocardiogram which were seen subsequently in a patient of Dr. Herrick diagnosed as dying from coronary occlusion verified by autopsy.

Since arteriosclerosis, hypertension and coronary heart disease are responsible for the great majority of deaths in the Western world, the attention of physicians and scientists during the past twenty years have been focused on the elucidation of the different problems involved. Great advances have been achieved during the last twenty years, but much remains to be known. We now know that myocardial infarction is produced by coronary obstruction but we also know that sometimes a myocardial infarct takes place without any demonstrable coronary occluson. It is, however, accepted even during the era of Osler and Albutt that myocardial infarction is associated with some disease of the coronary arteries. Osler, for example, classifies *Angina Pectoris* into three categories:

1. *Mildest Form* (*Formes Frustes* of the French). Feeling of distress or uneasiness and substernal tension, without any actual pain.

2. *Mild Form* (*Angina Minor*). Substernal pain of moderate severity with radiation to the arms. Seen in nervous, hysterical persons, in tobacco smokers, and after acute infections especially influenza. More common among women and is never fatal.

3. *Severe Angina* (*Angina Major*). Characterized by severe retrosternal pain (*dolor pectoris*) and feeling of anguish and sense of imminent death (*Angor animi*).

He describes extrapectoral features of the pain as well as pulmonary and cerebral manifestations. In the majority of cases there exists organic disease of the heart or blood vessels and there is always liability of sudden death. The pain lasts

from a few seconds to two minutes. It is provoked by muscular effort, mental emotion and flatulent distention of the stomach. There is hypersensitivity to cold such as chill in getting out of bed or from a bath.

We have always associated angina pectoris with EFFORT, so much so that we often call this disease "angina of effort", suggesting effort as the most important and most specific provocative agent. We have seen, however, many patients dying of coronary artery disease while resting in bed or during sleep. May it not be pertinent to ask the question of whether or not anginal attacks during rest or during sleep may indicate myocardial infarction rather than angina of effort? Parkinson has already stated that one may diagnose coronary occlusion when a man of advancing years is seized while *at rest* with severe pain across the sternum which continues *for hours* and is accompanied by shock. May we not postulate the possibility that sudden occlusion of the coronaries takes place during resting periods because the circulation is sluggish and therefore the coronary flow is also slower, hence conducive to the formation of intravascular clot, especially in the presence of atheromatous plaques in the coronaries? Furthermore, when the circulation is sluggish in the presence of partial occlusion of the coronaries due to atheromatous plaques, the collateral circulation is not primed for immediate use and remains dormant in a potential state. Early ambulation and appropriate exercise as an essential part of the treatment of myocardial infarction has been one of the foremost therapeutic triumphs in recent years that saved many lives which otherwise would have been lost.

The pathogenesis of atherosclerosis has been linked from the old days with deposition of fat in the intimal coat of the arteries. Osler classified arteriosclerosis into three classes:

1. *Nodular.* Atheromatous plaques.
2. *Diffuse.* Increase of subendothelial layer with atheromatous plaques, hypertrophy of the muscular coat. hypertrophy of the heart and fibrous myocarditis.
3. *Senile.* Monckeberg type in smaller arteries and calcification of the aorta.

He defined arteriosclerosis as thickening of the arterial coats with degeneration, diffuse or circumscribed, and mentioned the following as the etiologic factors:

1. Hypertension
   a) Hyperpiesis
   b) Arteriosclerosis with kidney and heart disease
   c) Kidney disease
2. Old age
   a) Genetic
   b) Amount of wear and tear
3. Chronic intoxication: alcohol, lead, gout, infections
4. Syphilis
5. Overeating
6. Stress and strain of modern life
7. Overwork of muscles
8. Renal disease

It is thus clear that arteriosclerosis was not quite clearly understood as late as 1918 when Osler wrote the eighth edition of his book. I do not wish to convey the impression that we fully understand this disease today, but wish merely to point out that we have been able to discern more clearly the different types of arterial disease and describe more definitely the characteristic histopathological changes in each case. Thus we consider the term "arteriosclerosis" as a generic word to include three distinct types of arterial disease. These types essentially conform with the types recognized by Osler but now more definitely described and better understood. These three types are:

1. *Atherosclerosis.* Affecting mainly the large arteries: the aorta and its immediate branches; the coronaries and the cerebral arteries. There is plaquelike intimal deposits *containing lipids.* The lumen of the artery affected is narrowed leading to closure.
2. *Medial calcific sclerosis.* Involving primarily the muscular arteries, particularly the legs. There is local calcification and fibrosis of the media "pipestem" vessels. The lumen is not specially narrowed, cal-

cification on X-ray and no specific clinical symptoms.

3. *Hyperplastic arteriopathy* (*arteriosclerosis*). It affects the systemic small arteries and arterioles, particularly the renal. Pulmonary vessels may be involved if there is pulmonary hypertension. It is associated with or resulted from increased arterial pressure.

The above classification obviously shows that of the three types, *atherosclerosis* is the one most primarily involved in myocardial infarction. Occlusion of the coronary artery may take place in any one of two ways:

1. Gradual and partial occlusion resulting in coronary insufficiency and diffuse myocardial fibrosis, or
2. Sudden and complete obstruction resulting in myocardial infarction.

The sudden and complete occlusion of the coronary artery may take place in any one or a combination of the following ways:

1. Complete occlusion of the lumen by an intact atheroma
2. Thrombus formation on a ruptured atheroma.
3. Occlusion of the ostia of the coronaries by syphilitic lesions in the aorta.
4. Occlusion by an embolus from a detached vegetation from a valve.

The most frequent type of coronary occlusion observed in the Philippines is that associated with atherosclerosis. From time immemorial degenerative changes in the coats of arteries were believed to be influenced by genetic (hereditary) factors, amount of daily wear and tear, overeating and stress and strain of modern life. Because of the fatty nature of the atheromatous nodules there has been a tendency during recent years to emphasize the role played by the dietary intake of fats and oils especially because statistical figures seem to point out the prevalence of atherosclerosis among individuals showing high cholesterol blood levels. Hypercholesterolemia,

atherosclerosis and coronary occlusion is the most popular combination accepted by most physicians to explain the pathological processes that lead to myocardial infarction. The weight of available evidence today seems to support the view that in the process of atherogenesis, the initial lesion is biochemical followed later on by the histological changes in the arterial wall. The lipophages or foam cells that are found in the subintimal layer of the atheromatous arteries are different from the lipocytes or adipose tissue cells. The lipocytes contain almost exclusively neutral fat and serve as sites for storage, synthesis and metabolic transfer of fatty acids, while the lipophages contain lipoproteins. The foam cell is not peculiar to the atheromatous lesion but is an ordinary pathologic phenomenon found in a variety of lesions such as degenerating tumors, removal mechanisms when hemorrhage occurs in tissues, xanthelasmas of lids, xanthomas of skin and tendons, arcus senilis of the cornea, lipoid pneumonia, Nieman-Pick and Gaucher's disease. Experimentally the injection of cholesterol suspensions subcutaneously provokes foam cell formation. These facts suggest that the foam cell is a characteristic tissue reaction to an *excess of lipid molecules.* We may therefore postulate that before lipid deposition takes place there must be first an excess of lipid in the blood. The serum lipids are classified into two types:

1. The Lipoproteins, and
2. The Free (Non-esterified) Fatty acids.

The Lipoproteins contain cholesterol (free and esterified), phospholipid, glyceride, protein and water. The Lipoproteins have been classified into alpha and beta lipoproteins depending upon their behaviour in the ultra-centrifuge and their electrophoretic migration. The alpha-lipoproteins have a smaller molecule, a higher density and contains around 40% lipids. The beta-lipoproteins contain 75% or more lipids, have a larger molecule, a lower density, and are affected by diet, fasting, age, gonadal hormones and other influences. In fasting states and when carbohydrate utilization is decreased as in diabetes mellitus the beta lipoproteins in the serum is increased. Of the three major sources of nutrients, amino acids, sugar and fatty acids only the fatty acids present a problem of water solubility. The biochemical changes in our system

take place in a watery solution; since fatty acids are hydrophobic, that is, they are immiscible and insoluble in water, nature must evolve mechanisms to be able to absorb, transport and utilize fatty acids and other lipids. These mechanisms consist of emulsification, chemical combinations with substances containing hydrophilic groups and complex formations with substances conferring greater water miscibility and dispersibility, like bile salts and proteins. The esterified fatty acids in the blood are carried within lipoprotein molecules, but have the chemical and physical property of a protein molecule. The beta-lipoprotein molecule has enough protein to cover only one-half of its surface. The free fatty acids comprise less than 10% of the fatty acids in the blood plasma. They are not exactly free because they are bound to albumin. The dietary fat enters the systemic circulation through the intestinal lacteals and the thoracic duct in the form of *chylomicrons* (so-called because they consist of chyle particles one micron in diameter). They are composed mainly of neutral fat with small amounts of phospholipid, cholesterol and protein. After they are released into the systemic circulation from the thoracic duct they are rapidly removed by the liver and extrahepatic tissues. When excess carbohydrate is available, that is, during hyperglycemia, the chylomicrons are shunted largely to the fat depots. Hormones influence the transport and utilization of lipids; insulin inhibits release of fatty acids from depots. Somatotropic (growth) hormone, epinephrin and norepinephrin accelerate the mobilization of free fatty acids. Androgen administration causes a rise and estrogen a fall in beta-lipoprotein.

The principal steroid in the diet is cholesterol. Recently cholesterol has received a preferential attention in the pathogenesis and is involved in the transport of glyceride. Fatty acids, glycerol and phospholipids are readily metabolized or rapidly degraded. The steroid nucleus of cholesterol is not degraded although its side chain may be oxidized with formation of bile acids and certain hormones. A normal person synthesizes around 1.5 grams of cholesterol per day 79% of which is excreted as bile acids and a portion of the remainder excreted as cholesterol in the feces. Now, cholesterol is an essential part of the beta-lipoprotein molecule and lipopro-

teins are involved in glyceride transport, hence when more lipid is transported, more lipoprotein vehicles are synthesized, and necessarily more cholesterol is manufactured. The liver is the major site for the synthesis of cholesterol and lipoproteins. It is easy to understand, therefore, the reason for the great emphasis laid upon the role of cholesterol in the pathogenesis of hyperlipemia and atherosclerosis.

Summarizing the dynamics of serum lipids we find the following:

1. The lipids circulating in the blood are:
   a) Lipoproteins (alpha, beta) and dietary chylomicrons
   b) Free fatty acids bound to albumin
2. Sources:
   a) The fat depots release free fatty acids and triglyceride
   b) The intestines supply the chylomicrons
   c) The liver supplies the lipoproteins
3. The liver receives free fatty acids, chylomicrons and carbohydrate from the systemic circulation to synthesize the lipoproteins.

Hereditary and environmental factors exert a decisive influence on serum lipids. Gross abnormalities of serum lipids are observed in some genetic disorders like familial (primary) hypercholesteremia and essential hyperlipemia. The following environmental factors have conditioning effects on the patterns of serum lipids among individuals:

1. Diet
2. Stress
3. Certain diseases: nephrosis, hypothyroidism, diabetes, biliary cirrhosis, portal cirrhosis, pancreatitis, gout.

Sex also has a definite influence on serum lipids.

To define what is the normal serum lipid or the normal cholesterol will be a very difficult task in view of the above considerations. It should appear much simpler to speak of

abnormal conditions of serum lipids and cholesterol. The range of cholesterol blood levels among Americans is 107-320 mgs% with a mean of 200. For Filipinos the range is 73-353 mgs% with a mean of 180 mgs% as determined by Camara-Besa *et al.* (1) in men of the armed forces of the Philippines.

Although myocardial infarction is essentially linked with atherosclerosis of the coronary artery, one cannot draw the conclusion that a person suffering from atherosclerosis will necessarily suffer from myocardial infarction. In West Africa, Abraham *et al.* (2) found hypertension and atherosclerosis to be a prevalent disease among the native Negroes but the incidence of myocardial infarction was practically nil. The prevalent complications of hypertension and atherosclerosis found by them are cerebrovascular accidents, heart failure, and renal failure. They did not find any case of acute myocardial infarction. It is also a well known fact that the blood cholesterol levels among them was low, around 100 mg. and yet the incidence of hypertension, atherosclerosis and cerebrovascular accidents was the same as that found among the whites in the United Kingdom.

The high fat diet of the Americans has been blamed by American workers led by Ancel Keys to explain the high rate of hypertension, atherosclerosis, hypercholesterolemia and myocardial infarction among them and yet hypertension, atherosclerosis, hypercholesterolemia and myocardial infarction are found in increasing numbers among Filipinos not only among the higher well-to-do class but also among the lower classes whose diet is sadly deficient in fat and protein. On the other hand, we cannot close our eyes to the influence of a high fat diet in the pathogenesis of atherosclerosis and coronary artery disease because during the last world war, when the European diet was very deficient in fat, the incidence of coronary artery disease in European countries was remarkably much lower than that during the pre-war period. These observations pose the following paradoxical situations:

1. High fat diet leads to high cholesterol, atherosclerosis and myocardial infarction.
2. Low fat diet leads to low cholesterol, atherosclerosis without myocardial infarction.

3. High fat diet, high cholesterol (Eskimos)(3) that do not lead to atherosclerosis and/or myocardial infarction.

These conflicting observations clearly indicate that we have unwittngly failed to understand the essence of the problem of atherosclerosis and myocardial infarction, and in our eagerness to simplify the concepts involved we point our finger to cholesterol as the villain and to high dietary fat as the principal accomplice. There is not the least doubt that there are many different factors involved in the pathogenesis of both diseases, but no combination of such factors, or all of them put together will produce artherosclerosis or myocardial infarction, unless some other unknown factor exerts its influence; in other words, all these different roads that lead to these two diseases, must finally converge into a common pathway, to give rise to atherosclerosis and/or myocardial infarction. All indications seem to point out that this unknown mechanism must be sought in the biochemical changes that take place in the process of atherogenesis. Until this riddle is solved we will continue groping in the dark, falling in the pitfalls created by oversimplification and finally resorting to fallacious rationalization in our attempt to extricate ourselves from the series of contradictions we have incurred. The present status of our knowledge leads us to draw identical conclusions from contradictory premises, and this is obviously absurd.

Today, we unvariably associate myocardial infarction with acute ischemia of the myocardium. Certain experiments, however, performed by Bulle *et al.* (4) have shown that myocardial necrosis indistinguishable from that seen in myocardial infarction can be produced by perfusing the rabbit's heart with histamine or serotonin solution. Such lesions are preventable by chlorpromazine. Also, Hans Seyle (5) described similar lesions in experimental animals produced by certain electrolytes (Na, PO_4, SO_4, ClO_8), after sensitizing the myocardium with corticosteroids. These authors have opened a new frontier which should be thoroughly explored for a better understanding of this disease.

We are all acquainted with the numerous cases of patients dying suddenly from typical cardiac infarction showing on

postmortem examination no trace of acute coronary occlusion despite the most painstaking search. Since such instances occur in individuals in the middle or past middle age, there is usually seen a certain degree of atherosclerosis of the coronaries, but not necessarily more severe than in patients of the same age who do not suffer from an acute heart attack. It is not easy to claculate the frequency of this condition, but it has been estimated to be around 30%, some authors (6) reporting an incidence as high as 59% while others (7) as low as 16%. During the recent Korean war many soldiers in the prime of life who were killed in combat showed typical lesions of myocardial infarction at autopsy without any evidence of coronary occlusion.

In view of the above considerations, may we not reexamine the whole problem of atherosclerosis and myocardial infarction, and postulate that myocardial infarction is a disease entity, separate and different from cerebrovascular disease, atherosclerosis and hypertension, with its peculiar characteristics, in which hypercholesterolemia and atherosclerosis are just one of the many varied elements that condition the heart muscle to the necrotizing action of a common agent or agents via a common mechanism? I therefore would like to invite the attention of all students of cardiology to exert all our efforts to help find this essential UNKNOWN FACTOR without which myocardial infarction can not occur, even though all the other factors are in operation, such as diet, genetic, stress, atherosclerosis, hormonal, certain diseases and finally cholesterol. Thus we will be in a better position to harmonize the conflicting mechanisms and contradictory concepts that we are forced to accept whenever we ascribe the prevalence of coronary artery heart disease to high fat diet and hypercholesterolemia.

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