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Coronary Thrombosis: A New Concept of Mechanism and Etiology

Evidence is presented in support of the theory that this disease is brought about by a nutritional deficiency, rather than surplus of fat in diet

W. J. McCORMICK, M.D., *Toronto, Canada*

Coronary thrombosis is defined as a clotting of blood in the coronary arteries of the heart, caused usually by a slowing of the circulation or changes in the blood or blood-vessel walls. This thrombotic lesion usually results in occlusion of the involved artery and sudden death from myocardial ischemia.

A brief survey of the pathology of vascular thrombosis in general may help to clarify the problem. Ziegler,[1] in his monumental work on general pathology, states that "The three major causes of thrombosis are: retardation of the blood current, local changes in the blood-vessel wall, and pathological changes in the blood itself," and that "One of these factors alone does not ordinarily cause thrombosis." He further states that "When the intima is injured by compression or crushing, or by irritant chemical agents, we may observe blood platelets adhering to the vessel wall at the injured point and soon they cover the site of the injury in several layers. Then red blood corpuscles and leucocytes may separate from the circulation and join in the deposition. Under favorable conditions the thrombus thus formed may undergo organization by the invasion of sprouting capillaries and endothelial fibroblasts from the intima, thus forming healthy granulation tissue and consequent healing by cicatrization, with consequent contraction, so that in time the lesion may appear as merely a thickening of the vessel wall." More often, however, under present conditions, the granulating thrombotic tissue fails to cicatrize and takes on the nature of "proud flesh," this building up erratically effects complete occlusion of the blood vessel, which, in the case of the coronary artery, usually results in sudden death or a slowly resolving infarction of that portion of the myocardium involved.

1. Ziegler, E., General Pathology, 8th edition, William Wood & Co., 1900.

PREDISPOSING FACTORS

In the extensive literature regarding thrombosis and atherosclerosis it is found that the recognition of a disturbance in the intercellular ground substance of the arterial intima is common to all. This collagenous break-down of the so-called "cement of life" results in instability and fragility of the connective-tissue components of the intima, and may give rise to intimal or subintimal hemorrhage, involving the vasa vasorum, and resulting in thrombogenesis.[2,3,4] In 1941 Paterson,[5] in a series of autopsies on coronary thrombosis cases, frequently found a capillary hemorrhage at the site of the thrombosis, which he regarded as an etiological prelude resulting from deficiency of vitamin C. In support of this conclusion he found that 81% of coronary cases in hospital practice had a subnormal blood-plasma level of ascorbic acid, compared to 55.8% in a corresponding group of general public-ward cases. Accordingly he suggested that coronary patients be assured of an adequate intake of this vitamin. Other forms of local injury to blood vessels acting as precursors to thrombotic lesions are reported by Josue,[6] who found that repeated intravenous injections of adrenalin caused vascular thrombosis, and by Solowjew,[7] who found that local cauterization precipitated thrombosis, and by Taylor,[8] who found that local freezing had a similar effect. More recently Willis,[9] in a study of atherosclerosis, concluded that the mechanical stress applied in the stretching of an arterial wall was a predisposing factor in the development of thrombi, and Burton,[10] showed that 4 factors contributed to the stretching: blood pressure, surrounding tissue support, radius of the artery, and curvature of the artery.

2. Aschoff, L., Lectures on Pathology, Paul B. Hoeber, Inc., 1924.
3. Duff, G. L., *Arch. Path.*, 20:81,1936.
4. Moon, H. G., & Rinehardt, J. F., *Circulation*, 3:481,1952.
5. Paterson, J. C., *Canad. M. A. J.*, 44:114,1941.

VITAMIN C DEFICIENCY

Counteracting these stresses are the tissue components of the arterial wall, and all such stresses increase the local need for adequate vitamin C to maintain the stability and integrity of the connective tissue involved. Willis[9] has also shown that scurvy (or extreme deficiency of vitamin C) in guinea pigs is effective in producing thrombotic lesions which are morphologically identical with those of the human disease. In earlier studies of blood vessels under deficiency of vitamin C, Laseque and Legroux,[11] in humans, and Findlay,[12] in experimental animals, found fat deposits in capillaries and small

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7. Solowjew, A., *Ztschr. f. d. ges. exper. Med.*, 69: 94,1929-30.
8. Taylor, C. B., et al., *Arch. Path.*, 49:623,1950.
9. Willis, G. C., Report Annual Meeting and Proceedings, R. C. P. & S. of Canada, Oct. 30-31, 1953.
10. Burton, A. C., *Am. J. Physiol.*, 164:319,1951.
11. Laseque, C. & Legroux, A., *Arch. Gen.*, 2:680. 1871.

veins. Koch[13] observed hyaline degeneration and fat deposits in the arteries of human scurvy victims, and Lamy et al.[14] reported widespread atherosclerosis and arterial thrombosis in young people among fatal cases of malnutrition in prison camps which certainly were not cases of cholesterol over-feeding. It is thus obvious that deficiency of vitamin C plays a major role in the pathogenesis of thrombotic disease.

RESTORATION OF COLLAGEN WITH VITAMIN C

It is of interest that in normal vitamin-C status the intercellular cement substance (collagen) which normally maintains the cohesive stability of connective tissue generally, including the blood vessels, becomes semiliquid under pronounced deficiency of this vitamin, as reported by Wolback and Howe,[15] and its glycoprotein constituent is released into the blood stream. The normal adhesive status of this cement substance is quickly restored by administration of vitamin C, as shown by Wolbach.[16] It should also be noted that an increase in serum - glycoprotein is found in many disease conditions, including the rheumatic diseases, traumatic and hemorrhagic shock, burns and cold, physical injuries, infections, cancer and myocardial infarction.[17,18,19,20,21] It is equally noteworthy that a definite deficiency of vitamin C is found in these same conditions, as well as a tendency to concurrent thrombotic disease. Woolling and Shick,[22] of the Mayo Clinic, have recently reported the frequent concurrence of cancer and thrombosis.

CHOLESTEROL

Much attention in recent years has been given to the possible role of fat metabolism in thrombotic disease. This perhaps had its origin in the fact that cholesterol crystals are usually found as a component of the thrombus, but this is to be expected as it is a normal constituent of blood, bile, nervous tissue, egg yolk, and all animal fats and oils. Albumin is also a normal constituent of all body tissues, and of thrombi; but a high-protein diet has not been incriminated. It is true that higher blood levels of cholesterol are found at times in thrombotic disease, but this could be coincidence, a possible third unrecognized element being the common factor. Biskind[23] claims that deprivation of the B and C vitamins, or their depletion in the liver by detoxication of exogenous poisons, may result in liver damage and loss of its ability to metabolize choiesterol, with consequent high blood levels of same. He states that "patients so affected are usually advised not to eat liver, eggs and other cholesterol-rich foods, and this interdiction further impairs nutritional status. When these patients are placed on a regimen combining the available crystalline vitamins and desiccated or cooked whole liver, there is usually a dramatic reduction in blood cholesterol despite the greatly increased intake." Furthermore, Willis[9] has found that the feeding of cholesterol to animals causes a depletion of vitamin C, and he suggests that this may indirectly produce injury of the intimal ground substance and consequent thrombosis. This concept is supported by the observation of Reid,[24] that parenteral injection of vitamin C inhibits experimental atherosclerosis in both scurvy and cholesterol feeding.

BRITISH OBSERVATIONS

With further reference to cholesterol, Duguid[25] says: "Nevertheless the incidence of coronary disease did not seem to decline in this country (Great Britain) during the war when our intakes of fats was restricted, nor, for this matter, do rabbits with cholesterol lesions die of coronary thrombosis." He submits evidence that atherosclerosis may be caused by thrombosis, rather than vice versa. He concluded that the atherosclerotic foci were produced by the break-down of older and more deeply buried deposits (repeated layers of mural thrombi). He further states that "in cholesterol-feeding experiments far more cholesterol is needed to produce lesions than is ever likely to be produced from a normal human diet." Wolffe[26] says: "A high fat and high cholesterol intake is no more the cause of atherosclerosis than a high carbohydrate intake is the cause of diabetes mellitus," and that the routine use of anticoagulants is still open to question.

EXPOSURE TO STRESS

The stress of modern life, another factor predisposing to coronary disease, could act by increasing the body requirement of vitamin C. Any noxious stimulus increases production of epinephrine, and this in turn causes depletion of vitamin C in the adrenal gland.[27] Exposure to the stress of surgery may act in this way to cause a fall in the blood level of vitamin C,[28] which could account for the development of postoperative thrombosis. It has also been shown that the noxious stimulation of the sensorium of the respiratory system by tobacco smoke, by acting on the adrenal gland, releases epinephrine, thereby temporarily increasing blood sugar[29] as a protective response of the organism,[30] while at the same time accentuating deficiency of vitamin C.

From these data it would seem that coronary thrombosis may be a deficiency disease rather than one of surfeiting, and that the deficiency is mainly that of vitamin C. Long continued deficiency of vitamin C would lead to weakness and fragility of connective tissues generally, and in this case the coronary arteries in particular, resulting in stretching and consequent hemorrhagic lesions of the intima. The reaction of the organism is the deposition of a thrombus at the site of injury. This thrombus under normal conditions should develop into normal scar tissue, but the deficiency which caused the initial intimal lesion prevents such conversion resulting in an ineffectually organized thrombus, with occlusion of the artery.

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TOBACCO

It would seem paradoxical that deficiency of vitamin C should prevail where fresh fruits rich in this vitamin are so abundant and where scurvy is thought to be a disease of the past. But, of thousands of chemical tests on human adults to determine body level of vitamin C, 90% were found deficient. Our infants and young children are better provided for in this respect. Great deterioration comes from candy, soft drinks, etc. in childhood, and early adult life. Tea, coffee, tobacco and alcohol further distorts the normal nutritional pattern. Tobacco smoking, the greatest despoiler of vitamin C, depletes the body of the vitamin by the adrenal reaction, and the toxins of the smoke have a destructive action on the stored vitamin. Vitamin C is chemically a potent reducing and oxidizing agent, and when taken internally it reacts with the circulating smoke poisons, resulting in reciprocal neutralization. Over ten years ago, in laboratory and clinical tests, it was found that the smoking of one cigarette, as ordinarily inhaled, destroyed the vitamin-C content of an average orange. This observation was confirmed by researchers in the United States[31] and in Poland. This finding precludes the likelihood of any steady smoker attaining an optimal body level of this vitamin from dietary sources. In hundreds of chemical tests for vitamin-C status in smokers a normal level of this vitamin has yet to be found.

In a study of 151 fatal cases of coronary thrombosis,[32] 97% had been smokers—58% heavy smokers, average age at death 47 years; 42% light or moderate smokers, average age at death was 58½ years. In a recent Amercian Cancer Society survey of 187,000 men of 50 to 70 years, the number of deaths from coronary heart disease was found to be almost twice as high in the cigarette smokers as in the non-smokers.

Buerger's disease, or thromboangiitis obliterans, first recognized 50 years ago, involves the peripheral arteries of the extremities in multiple thrombotic lesions in the vasa vasorum ultimately leading to arterial occlusion and gangrene. Amputation of the affected extremities and interdiction of smoking is the usual treatment. This disease, like coronary disease, showed a marked predilection for males in early reports, but recently a marked leveling off in sex incidence has been noted. Regarding the etiology Silbert[33] says: "The importance of tobacco as the exciting cause of this disease must be stressed. In over a thousand instances of this disease studied by the writer a typical case in a non-smoker has not been seen. Cessation of smoking regularly arrests the disease, while continued use of tobacco is coincident with progression. . . .In several early cases of the disease, cessation of smoking, without any treatment whatever, has resulted in disappearance of all symptoms." Buerger's disease is not infrequently concomitant with coronary thrombosis. Lewis[34] says: "It is to be recognized that in these patients tolerance of exercise may be masked by breathlessness or anginal pain; this, by limiting the exercise taken, will conceal a weakness of the legs, just as, reversely, a severe intermittent lameness may conceal angina of effort by prohibiting the amount of exercise necessary to induce it."

SEX RATIO OF INCIDENCE

The sex incidence of coronary disease is also suggestively significant. Levine[35] says: "The sex distribution of this disease is most striking, — a ratio of 3½ males to 1 female. It is difficult to explain the great frequency of coronary thrombosis in the male . . . a factor may be the possible role of tobacco . . . Certainly the consumption of tobacco has been in the past almost entirely confined to men. A more definite answer may be apparent before long if the coming generation of women continue the smoking habit that has become so general." This forecast was made in 1929 and already the answer seems to be in evidence. Prior to 1929, the sex ratio of incidence of coronary thrombosis was estimated as high as 7 males to 1 female. Recent figures (Toronto Health Department) indicate this ratio to be 2 males to 1 female.

The rising incidence of coronary and other forms of thrombotic disease has followed closely the increase in tobacco consumption. Cigarette consumption in Canada was 5 billion in 1935 and 25 billion in 1955, an increase of 500%. In this same time the population has risen 40%. A parallel situation prevails in the United States where the tobacco consumption per capita is double that of Canada. During this period the incidence of coronary thrombosis, Buerger's disease and post-operative thrombosis has shown a closely proportionate increase. There has been no such increase in the consumption of cholesterol-rich foods during this period.

SUMMARY

The author submits evidence in support of his belief that thrombosis is not in itself a pernicious development, but rather a protective response of the organism, designed normally to effect repair of damaged blood vessels by cicatrization. High blood pressure, excessive stretching of blood vessels, and deficiency of vitamin C, resulting in rupture and bleeding of the intima at the site of such stress initiate the development of the thrombus by means of the clotting of the blood, which is also a protective reaction. This multiple protective mechanism should be sustained and controlled by physiological means (vitamin-C-therapy) rather than suppressed by anticoagulants with their dangerous side effects.

The author believes that an optimal body level of vitamin C offers the best natural means of effecting healthy scar tissue, and claims that the initial intimal hemorrhage precipitating thrombosis would not occur if adequate prophylactic use of this vitamin were made in advance, and furthermore, that the thrombosis, if already forming, would thus have been more readily converted to healthy scar tissue with consequent contraction, thus precluding the development of occlusion with its dire results.

A close parallel is drawn in the incidence and pathology of coronary thrombosis and Buerger's disease, and the increasing incidence of these diseases is statistically related to the universal use of tobacco, which the author claims is the major factor in accentuating vitamin-C-deficiency.

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