Unitarian Concept of Pathogenesis of Myocardial Infarction

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Coronary atherosclerosis, coronary thrombosis and myocardial infarction are believed to be the expressions of the same pathological process and are thus considered to represent a continum from coronary atherosclerosis through coronary thrombosis to myocardial infarction. Such stereotyped thinking has overshadowed other viewpoints which may deviate from contemporary thought and belief. It is proposed that these three processes are distinct entities which, though often associated, are neither wholly interdependent nor represent various stages of a continuum.

During the last serveral years, many risk factors have been well defined as associated with conorary artery disease. Such risk factors as have found more universal acceptance are:

1. Heredity
2. Hyperlipidaemias
3. Hypertension
4. Diabetes mellitus
5. Smoking
6. Obesity
7. Sedentary occupations
8. Lack of physical activity
9. Stress
10. Type A personality
11. Over-work.

Recently, cholrinated water and excessive intake of sugar have been incriminated as the determinants of coronary artery disease. It seems perhaps unfair for every one to beat his own trumpet and infer causality from mere association. To prove the cause and effect relationship, there should be consistent association without exception. Besides all the factors defined as risk factors must find expression through a common final path.

Raised blood cholesterol is the most favoured risk factor blamed for the occurrence of cornary artery disease. It is argued that most patients who suffer from coronary artery disease show evidence of hypercholesterolaemia. It is guoted that during second world war, the incidence of myocardail in farction fell considerably in Europe which was the theatre of war and where poverty and deprivation during the period forbade the use of cholesterol rich diets which were expensive and beyond the reach of ordinary man. It is argued that, though stress was universal in the extreme degree, the incidence of myocardial infarction fell providing adequate reason to exclude stress as concerned with coronary artery disease. One may submit that stress finds its expression through the liberation of catecholamines. Catecholamines are formed from tyrosine, an essential aminoacid, as given below:—

Tyrosine

↓ Tyrosine hydroxylase

3, 4-Dihydroxy phenylalanine (DOPA)

↓ Aromatic-L-Amino Acid Decarboxylase

Dopamine (Dihydroxy phenylethylamine)

↓ Dopamine beta oxidase

Norepinephrine

↓ Phenylethanolamine-N-Methyl Transferase

Epinephrine

Since proteins are the most expensive item of diet, protein deprivation was most prevalent during war years. Absence or deficiency of tyrosine in diet so common during war years, therefore, resulted in marked diminution or synthesis of catecholamines. It was probably the lack of expression of stress through catecholamines which caused marked diminution of the incidence of myocardial infarction during war years. It is usually overlooked that atherosclerosis is a process which occurs over the course of many years. It does not occur all of a sudden or during a short period of 5 to 6 years as witnessed by the war. While incriminating hypercholesterolemia, it is not kept in view as to why all people showing raised blood cholesterol levels do not suffer from coronary artery disease. It was demonstrated during Korean War that almost all the American soldiers who fell and were subjected to autopsy studies showed atherosclerosis, some showing extensive and advanced lesions. Soldiering is an active and athletic profession. Occurrence of atherosclerosis in young physically active soldiers more or less exonerates lack of physical activity as an important determinant of coronary artery disease.

The problem, therefore, cannot be resolved unless we link all the factors through a unitarian concept embracing all the risk factors either by providing a common final path or through its expression in the form of various risk factors. Until such a viewpoint is proposed and proved, there is likely to be little progress in our understanding of the causation, hence, prevention and treatment of coronary artery disease.

Atherosclerosis

The main determinants of atherosclerotic plaque formation are velocity of blood flow, intimal reaction, peripheral vascular resistance, hypoxia and hyperlipidaemia (Fig. 1).

Atherosclerosis is probably a function of *blood flow* which because of its motion possesses kinetic energy producing mechanical stress on the walls of the blood vessels. The stress on blood vessels begins as the blood starts flowing in the foetal blood vessels. The effect of blood flow on the vessel wall depends on the mean velocity, peak velocity, rate of change of velocity, angle of origin of a blood vessel from the parent trunk, size, shape and geometry and morphology of the blood vessel. The angle of branching and size and shape of blood vessels, and structure of the vessel wall are inherited variables which may serve as markers for severity of coronary artery disease. The velocity of blood flow is maximal in the mid-stream (fig. 2). As the maximum flow stream strikes the main vessel at the point of branching, the flow of blood assumes the characteristics of a projectile flow within the continuous pulsatile streamlined flow. The projectile stream of flow strikes the inner vessel wall at a variable distance from the point of branching depending on the velocity of blood flow, relative size of the

parent vessel and the branch and the angle of the branch to the parent vessel. The point of impact of the projectile stream at the branch vessel is the area at the highest risk (fig. 3). The risk is further aggravated by the pulsatile instead of steady nature of the blood flow. Repeated trauma to the vessel wall is the main determining factor in the causation of atherosclerotic plaque. This view explains the universality of the atherosclerotic lesions by the time of adolescence or adulthood. The severity and rate of progress of such a lesion are modified by intimal reaction, hypoxia and peripheral vascular resistance. Heredity influences the evolution of atherosclerotic lesions by determining the intensity of tissue reaction to endothelial damage, angle of branching and size, shape and geometry of blood vessels and morphology of the vessel wall. *Hypoxia* may be caused by smoking, pulmonary dysfunction (ventilatory, distribution, diffusion and perfusion defects) and high altitude. Experimental studies incriminate carboxyhaemoglobin in the genesis of atherosclerosis. The concentration of carboxyhaemoglobin in heavy smokers approaches the levels witnessed in experimental animals as causative of atherosclerosis. This is supported by the correlation between carboxyhaemoglobin levels in smokers and the incidence of atherosclerotic disease (Kjeldsen, 1969). Smokers with carboxyhaemoglobin levels exceeding 5 percent appear to run twenty times higher risk of getting atherosclerosis than smokers showing carboxyhaemoglobin values less than 3 percent (Wald et al., 1973). Smoking, therefore, may inflict its vicious influence by causing hypoxia. The latter would impair the sodium pump causing cell swelling. It may be recalled that a cell is normally electronegative with potassium ions inside the cell and sodium ions in the interstitial fluid bathing the outside of the cell. Normally, the cell membrane is partially permeable to sodium ions. The ingress of sodium ions into the cell is followed by egress of the potassium ions into the interstitial fluid. The sodium ions, to maintain osmolality within the cell, draw water into the cell causing *cell swelling*. This sequence of events is prevented through the operation of sodium pump carried by membrane adenosine triphosphatase (A T Pase) which extrudes sodium from the cell with passive entry of potassium into the cell. This is an active process needing free energy for its full operation. Such energy is provided by the conversion of adenosine triphosphate into 3'-5' cyclic adenosine monophosphate (cyclic AMP) through the enzyme adenyl cyclase. Whereas the aerobic glycolysis liberates 38 moles of free energy, the anerobic metabolism releases only 2 moles for each mole of glucose metabolised. The cell under the influence of hypoxia, therefore, may not be able to generate adequate amount of free energy to propel the sodium pump with resulting cell swelling. A swollen cell is a *sick* cell and as such suffers from increased membrane permeability permitting the insudation of cholesterol into the subendothelial region and is more liable to wear out if subjected to the trauma of projectile impact of flowing blood. A consequence of hypoxia would, therefore, be endothelial cell swelling and sickness with its resulting disruption. The disruption of endothelial cell sets in motion several types of tissue reaction. It may stimulate the subendothelial smooth muscle cells so that their proliferation and hyperplasia may be an attempt to fill the endothelial breach. Their excessive proliferation may cause their projection into the lumen of the vessel as a mound which may be endothelialised in due course of time. In early stages, there may be no lipid in these plaques. Such fibrous plaques,

commonly found in seals and sea lions, very much resemble the atherosclerotic plaques found in man (Stout and Boborques, 1974). Lipid deposition may be due to insudation of cholesterol through sick endothelial cells (due to continuing and consistent hypoxia in smokers, in those living at high altitudes and in those suffering from chronic pulmonary dysfunction). This view point is in contrast to the prevailing cholesterol insudation—intimal smooth muscle proliferation hypothesis. Besides, the breach of endothelial injury may cause platelet adhesiveness and aggregation and clotting mechanisms to come into play. These may add to the bulk of the atherosclerotic plaque.

Raised peripheral vascular resistence and hence, raised blood pressure accentuates the evolution of atherosclerotic plaque by causing increased tension on the vessel wall. The atherosclerotic plaque is, therefore, a function of velocity of blood flow which is further influenced by *heredity*, *hypoxia* and *raised peripheral vascular resistance*. *Hyperlipidaemia* may contribute to the evolution of atherosclerotic plaque either directly or indirectly after cell swelling and endothelial damage occurs. Atherosclerosis may, therefore, be viewed as a degenerative process dependent on blood flow and as such a physiologic consequence of various parameters of velocity of blood flow and time. Its severity and evolution may be influenced by other factors such as heredity, blood pressure, hypoxia and hyperlipidaemia. The role of heredity may be modified or nullified by appropriate marriage counselling and family planning. *Velocity* of blood flow may be controlled by reducing myocardial contractility and heart rate by the use of beta blockers. Blood pressure being a quantity should be kept as low as is compatible with symptom-free living. Hypoxia may be subdued by interdicting smoking and preventing and treating pulmonary dysfunction. Various well-defined risk factors in coronary artery diseases have been already delineated. Their isolated association with myocardial infarction would serve no useful purpose in preventing and treating myocardial infarction. It is obvious that a unitarian concept tying all these factors would be the only acceptable channel to permit preventive programmes. It is proposed that the risk factors operate through increased catecholamine activity (fig. 4). Enhanced catecholamine activity may be due either to their increased synthesis and/or release or to increased end organ sensitivity to them (catecholamine). Stress, a consequence of social and psychologic determinants, acts through the hypothalamus by causing increased release of catecholamines. In smokers, there is reported to be increased release of catecholamines. Hypoxia is a biochemical stress and is characterised by increased catecholamine activity. Hypertensive patients are known to show positive cold pressor test which is an expression of increased catecholamine activity. In *diabetes mellitus*, there is high incidence of autonomic neuropathy. The denervated tissues are known to be highly sensitive to neurotransmitters. *Obesity and sedentary* workers respond to normal day-to-day stress with increased release of catecholamines. *Heredity* may determine not only increased synthesis and/or release of catecholamines but as well increased end-organ sensitivity to them.

It would be obvious, therefore, that all the coronary risk factors may operate through a common final path provided by increased catecholamine activity which may be due either to increased synthesis and/or release of catecholamines or to increased end-organ sensitivity to them.

Pulmonary dysfunction may influence the evolution of myocardial infarction in several different ways (fig. 5). It occurs in chronic obstructive pulmonary disease, smokers, obesity, sedentary workers and pulmonary hypertension. Lungs are a rich source of heparin and plasmin activator. A diseased lung would contribute reduced amounts of both these substances which contain and subdue the clotting processes. Normal lungs inactivate 30 percent of *norepinephrine* which may find systemic expression in the presence of diseased lungs. *Hypoxia*, a common consequence of pulmonary dysfunction, may cause cell swelling through impairing sodium pump. Pulmonary dysfunction, therefore, is an important contributory factor in the genesis of coronary artery disease.

The consequences of catecholamines embrace several determinants of coronary artery disease (fig. 6). Catecholamines increase blood cholesterol levels and raise blood betalipoproteins. This is probably facilitated by the stimulating effect of catecholamines on fatty tissue lipase liberating large amount of free fatty acids. Excess blood free fatty acid content increases the available acetyl-COA, which is the precursor of cholesterol synthesis by the liver. Conversion of acetyl COA to mevalonate, first step in cholesterol synthesis, takes place through two distinct pathways, one mitochondrial and the other extramitochondrial. The cholesterol synthesis occurs outside the mitrochondria through the catalytic action of HMG-COA reductase. The latter enzyme is inhibited during fasting and may be controlled by a feed-back system provided by blood cholesterol. HMG-COA may be stimulated by catechnolamines enhancing the synthesis of cholesterol. Catecholamines, therefore, would accentuate cholesterol synthesis both by increasing the blood free fatty acid level and by stimulating the enzyme HMG-COA. Catecholamines, thus, raise the blood level of FFA, cholesterol and betalipoproteins (low density lipoproteins transport most of the cholesterol in the blood). Hyperlipidaemia witnessed in coronary prone patients is probably a function of catecholamine hyperfunction.

Catecholamines increase platelet adhesiveness and aggregation and cohesion. Whether this is mediated directly, by contraction of platelet tubular system extruding adenosine diphosphate from dense granules or by raising the blood lipids is not clear. Increased adhesiveness and aggregation of platelets provide the background assistance in increasing the size of atherosclerotic plaque and in occasioning clotting on areas where plasminogen-plasmin mechanism for clearing the thrombi is not very efficient. Such, of course, is the case at the atherosclerotic plaque where overlying sick endothelium is not in a position to produce adequate plasminogen.

Catecholamines may influence the atherosclerotic plaque by causing dilatation of the coronary artery, which may affect the atheromatous plaque in three different ways (fig. 7).

The rigid atheromatous plaque does not dilate with the rest of the vessel wall resulting in a shearing movement between the plaque and the unaffected vessel wall causing:

(1) Bleeding into the atheromatous plaque with its consequent enlargement and further encroachment on the lumen of the affected vessel.
(2) Rupture of the endothelium setting the stage for thrombosis to occur.
(3) Extrusion of the plaque with its poultaceous material into the lumen of the vessel causing

coronary embolism distal to the area of fateful event or coronary thrombosis at the bare area of atherosclerotic plaque.

All these events may eventuate in partial or complete occlusion of the affected coronary artery. The progression of these three processes may be arrested or halted by the control of bleeding by the clotting mechanisms or by vasoconstriction induced by serotonin liberated from the platelets at the clotting site or by catecholamines. The attempts at thrombus formation at the site of endothelial breach or at the raw area left by the extrusion of the atherosclerotic plaque may be defied by plasminogen-plasmin mechanism and endogenous heparin.

Catecholamines have both chronotropic and inotropic effects on the heart. The chronotropic effect is occasioned by increasing the slope of the phase 4 of action potential of various pace-makers. The inotropic effect is evidenced by increased contractility of the myocardium. This is reflected in shortened systolic ejection duration, enhanced dp/dt and reduced end-systolic and end-diastolic volumes. Various parameters of increased contractility accentuate the velocity of blood flow. The increased contractile force of the myocardium would more effectively occlude the intramyocardial circulatory channels, so to say, by squeezing them. Markedly enhanced myocardial contractility. may therefore, starve the inner shell of myocardium (subendocardium) the most and may cause myocardial necrosis. This is further aided by increased oxygen consumption (MVO2) of the myocardium culminating from increased contractility, enhanced myocardial work and raised blood pressure from elevated peripheral vascular resistance putting increased impedance to systolic evacuation of the left ventricle or afterload. The elevated oxygen requirements not only cause cell swelling of the myocardium encroaching on the intramyocardial vessels but as well endothelial swelling further narrowing the lumen of the vessel thus initiating a vicious circle culminating in myocardial necrosis. If the catecholamine storm blows over before irreversible myocardial necrosis occurs, the myocardium may be spared and blood vessels restored to their pre-stress status by resolution of endothelial swelling.

That myocardial infarction is not due to coronary thrombosis is supported by the following observations (Roberts, 1974):—

1. In fatal coronary artery disease, thrombosis is rarely (in about 10 percent) encountered in patients dying suddenly and in those dying from sub-endocardial infarction.
2. Thrombosis is encountered only in about 55 percent of patients dying from transmural myocardial infarction (Roberts, 1971).
3. More than 70 percent of patients suffering from fatal transmural infarction with cardiogenic shock show coronary thrombosis whereas only 15 percent of patients without power failure syndrome associated with fatal myocardial infarction have coronary thrombosis (Walston et al, 1970).
4. The larger the area of infarction, the higher the incidence of shock (shock occurs when more than 40 percent of myocardium is non-functioning), the greater the frequency of coronary thrombosis.

These observations indicate that coronary thrombosis is not necessary for the occurrence of myocardial infarction. Infact, the failure to demonstrate coronary thrombosis in patients dying of myocardial infarction suddenly, in those dying of subendocardial infarction and in only

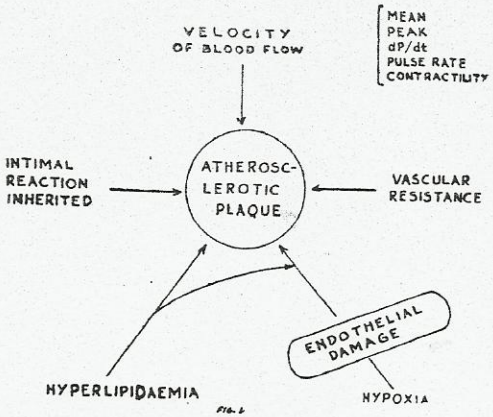

FIG. 1

FACTORS CAUSING ATHEROSCLEROTIC PLAQUE

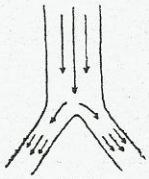

FIG 2

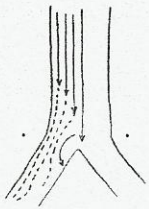

FIG 3

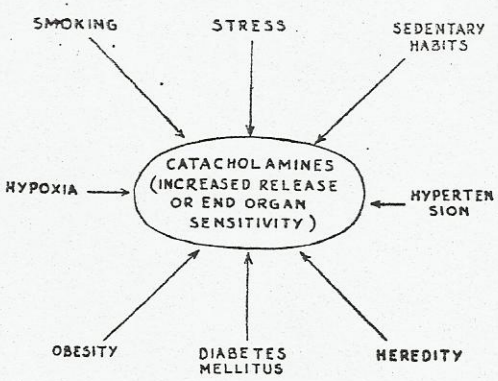

FIG. 4

CAUSES OF INCREASED CATECHOLAMINE ACTION

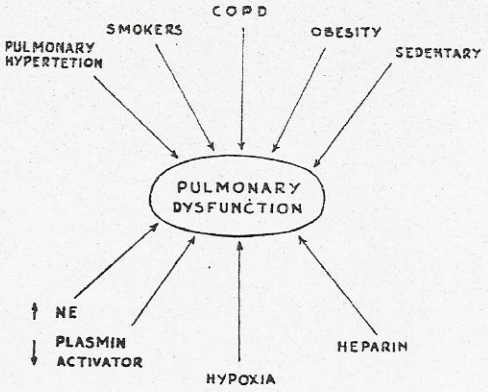

FIG. 5

CAUSES AND EFFECTS OF PULMONARY DYSFUNCTION

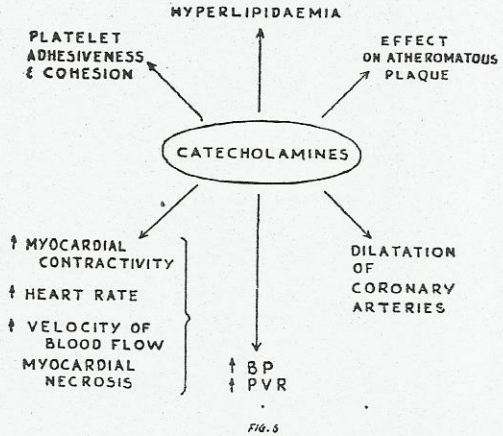

FIG. 6

EFFECTS OF CATECHOLAMINES

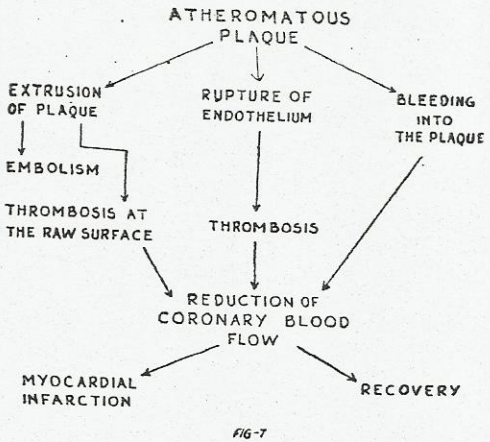

FIG-7

EFFECTS OF CATECHOLAMINES ON ATHEROMATOUS PLAQUE

50 percent of those dying from transmural infarction negates the causal contribution of coronary thrombosis in myocardial infarction. It may be that coronary thrombosis is a consequeence rather than the cause of myocardial infarction as is supported by the work of Erhardtet al. (1973) who demonstrated that administration of radioactive iodine labelled fibrinogen shortly after the onset of clinical myocardial infarction revealed radio-activity in coronary thrombi in patients with fatal myocardial infarction. This implies that the thrombus is formed after the onset of clinical and electrocardiographic myocardial infarction. The use of radionuclides such as technetium-99 m, potassium-43 and cesium-129 in locating and defining the extent of myocardial necrosis as cold defects may shed further light on the cause and effect relationship between myocardial infarction and coronary thrombosis. The occurrence of coronary thrombosis in most of the patients suffering from fatal myocardial infarction with cardiogenic shock is probably due to stasis of circulation, an important determinant of thrombus formation. Besides, shock increases blood coagulability and by increasing hypoxia, facilitates further endothelial cell swelling.

From the evidence available, it is likely that catecholamines play the villain of piece in the tragic drama of myocardial infarction. The pivotal role may explain the involvement of various risk factors in a unified whole. Angina pectoris or myocardial infarction with normal arteriogram)may be explained by catecholamines causing increased oxygen consumption and myocardial and endothelial cell swelling encroaching on the lumen of the blood vessels in the vulnerable area of the myocardium. Sudden death in clinical myocardial infarction without coronary thrombosis may be occasioned by catecholamines causing fatal dysrhythmias. Further, ischaemic cardiomypathy with normal coronary arteriogram may find explanation in terms of increased catecholamine activity causing relative myocardial ischaemia due to enhanced contractility and oxygen consumption. The swollen myocardial cells eventuating from impaired sodium pump due to hypoxia may cause myocardial dilatation providing the necessary stimulus for myocardial hypertrophy.

It is proposed, therefore, that atherosclerosis, myocardial infarction and coronary thrombosis are three distinct processes which though somewhat interdependent do not represent the facets of a continum. Atherosclerosis is a function of velocity of blood flow to which other factors such as heredity, hypoxia and hypertension contribute. Myocardial infarction is a consequence of catecholamine hyperactivity and is not due to coronary thrombosis. The latter infact ususally follows myocardial infarction complicated by cardiogenic shock and is hence a consequence rather than the cause of myocardial infarction.

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