CORONARY THROMBOSIS

The No. 1 Killer

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Since the beginning of the present century diseases of the heart and blood vessels have been steadily assuming a more prominent place in our vital statistics, and in this group we find coronary thrombosis in the lead - a greater cause of death than cancer, tuberculosis and diabetes combined. So rapidly has the mortality from this disease risen in recent years that it is now the principal cause of death for all past fifty years of age.

For some time the increasing toll taken by heart disease has been attributed to the increasing tempo and stress of modern life. Even the medical profession, which tops all other professions in mortality from coronary disease, is thus inclined to exonerate itself on the ground of the strenuous nature of modern medical practice. Recently, however, a more attractive explanation has attained general acceptance, the theory that our aging population, due to the average increase in life span, results in more people reaching the age in which diseases due to senility take their toll. Both these theories are conducive to medical complacency.

A striking example of this tendency was manifested in a public lecture in Toronto recently by a leading health authority in the statement that "there are few more creditable things for a city to have than a high cardiac death rate." In further explanation the speaker said: "The city with the best public health always has the highest cardiac death rate because the 'one-hoss shay' has to give out sometime, and it is the most natural way to pass out between 60 and 70," the implication being that in such a city a larger number of people must have lived to the age of 60 or more, at which time they would naturally be subject to general senile disintegration.

Unfortunately, however, this specious theory does not harmonize with the facts for the following reasons: (1) The type of heart disease, coronary thrombosis, chiefly responsible for the rising mortality, is not, strictly speaking, a senile disease, since it takes most of its victims between the ages of 45 and 55 years, and not a few below the age of 40, at a time when their mental and physical activities are at their best. In the case of the "one-hoss shay" it "went to pieces all at once and nothing first." (2) This theory does not explain the unprecedented increase in heart disease relative to pneumonia and cancer, both of which it has superseded as cause of death in recent years. Neither does it explain the higher female incidence relative to that of the male, which will be referred to later. (3) While it is true that the average span of life has been doubled in the last half century, this has been accomplished mainly by reduction in infant and child mortality as a result of better control of infectious diseases and improved feeding. Unfortunately, however, adult nutrition has not been materially improved, and the toll of degenerative diseases of middle life has not been reduced or postponed. Accordingly, post-65 life expectancy has only slightly increased. (4) The rate of increase in heart disease, particularly coronary thrombosis, has been disproportionately greater than the rate of aging of our population. Vital statistics of deaths of American physicians from 1933 to 1940 inclusive, indicate a rise in cardiac deaths from 33 per cent to 41 per cent of total deaths. Obviously the aging of the medical profession in this short time could not possibly account for such an increase particularly the relatively higher increase in coronary deaths from 3 per cent to 19 per cent in this same period. Neither is it reasonable to believe that improved methods in diagnosis could have brought about such a change in so short a time, since the electrocardiographic method of diagnosis has now been in use for fully forty years, and physicians as a rule have consultations with leading specialists in their own illnesses.

Fortunately not all physicians have taken such a rosy view of this rising tide of heart disease. Thirty five years ago Aikman (1) sounded a note of alarm in these words: "It is a well known fact that diseases of the heart and blood vessels have increased at an alarming rate in the last few years. Of course the stress of modern life is chiefly blamed, but it seems that there must be some other great etiological factor that works in such a slow and insidious fashion that it is not easily recognized."

In an effort to discover the nature of this insidious causal factor I have made a survey by means of a questionnaire mailed to the widows or next of kin of middle-aged males who have recently died sudden ly in the Toronto district, assuming that may of these would be coronary thrombosis cases. It was thought that the widows of these men would be best qualified to supply detailed information regarding their personal living habits, – diet, exercise, use of narcotics, age, height, weight, etc. After ruling out deaths due to accidents and infectious diseases there were 269 replies suitable for tabulation. Of this number 151 were found to be cases in which a definite diagnosis of coronary thrombosis had been made by the attending physician or coroner. The remaining 118 cases included non-coronary heart disease, cerebral hemorrhage, cancer, anemia, nephritis, diabetes, etc.

In the coronary-thrombosis group (151 cases) the average

age at death was found to be 52 years, the average weight was 168 lbs. Sixteen were 200 lbs. and over, one being 295. 94 per cent were reported as tobacco smokers and 6 per cent as non smokers at time of death. A further check on the latter elicited the fact that a number of them had discontinued smoking a month or so before death, either on their own volition or on medical advice. Fifty-eight per cent of the smokers were rated as "heavy smokers" and 42 per cent as moderate or light smokers. Fifty-five per cent were addicted to alcohol as well. The average age of the heavy smokers at death was 47 years, that of the moderate and light smokers was 58½ years, that of those addicted to, tobacco and alcohol was 47½ years (Apparently the addition of alcohol, as advised by some writers to counteract the vasoconstrictor effect of nicotine, did not prolong life in these cases). The two youngest in this group, who died at 27 and 29 years, were heavy users of both tobacco and alcohol.

In the non-coronary group as a whole (118 cases) the average age at death was 60½ years. Sixty-six per cent of this group were addicted to tobacco and 29 per cent to alcohol as well.

Regarding the nutritional habits of the coronary-thrombosis group, it was found that as a whole there was a marked tendency to deficient intake of the B and C vitamins, in that nearly all were predominantly white-bread users and low in their use of fresh fruits and salads. The ingestion of milk was also suboptimal, the principal liquids being tea, coffee, alcoholic and soft drinks.

DISCUSSION

The most striking feature in the above findings, and that providing the most obvious etiological clue, is the higher incidence of tobacco smoking and the use of alcohol in the coronary-thrombosis group, 94 per cent and 55 per cent respectively, as compared to the combined non-coronary group, 66 per cent and 29 per cent respectively. The breakdown of the age figures in the coronary-thrombosis group also provides evidence of the precipitating effect of narcotic addiction in this disease, the average ages at death being as follows: 47½ years for those addicted to both tobacco and alcohol, 52 years for those addicated to tobacco only, and 59½ years for those not addicted to either. The definite correlation of the life span and the degree of narcotic addiction is most significant, the heavier addiction being associated with a corresponding drop in average age at death.

A correlated study of other thrombotic disease processes may help to clarify the possible etiological role of tobacco. Another form of arterial thrombosis, known as thromboangiitis obliterans, or Buerger's disease, has long been recognized as being etiologically related to tobacco smoking. Silbert (2) says: "The importance of tobacco as the exciting cause of this disease must be stressed. The evidence in support of this contention is overwhelming. In over a thousand cases of this disease studied by the writer a typical case in a non-smoker has never been seen. Cessation of smoking regularly arrests the disease, while continued use of tobacco is coincident with progression."

The possible causal relationship between coronary thrombosis and Buerger's disease is shown by the closely parallel features in their symptomatology and pathology, as follows: (1) The greater susceptibility of the male; (2) The common pre-senile age incidence; (3) Periodic vasospasm, manifested in the former by anginal attacks, and in the latter by intermittent claudication with muscular pain and cramps; (4) Organic vascular changes, having their inception in Buerger's disease in the vasa vasorum, leading to progressive impairment in structure and function of the musculature proper; while in coronary thrombosis the initial changes occur in the coronary arteries, the anatomical counterpart of the vasa vasorum (viewing the heart as a muscular expansion of the vascular system), resulting in secondary changes in the heart muscle; (5) Thrombotic occlusion of the involved blood vessels, leading to gangrene as a final eventuality in Buerger's disease, and to infarction and necrosis in coronary thrombosis when not intercepted by a fatal termination in the initial seizure; (6) The two diseases are not infrequently concomitant. In reference to such cases, Lewis[3] 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 claudication may conceal angina of effort by prohibiting the amount of exercise necessary to induce the latter."

A partial explanation of the precipitating role of tobacco in thrombotic disease may be found in the well-recognized sympatheticoadrenal protective response to irritation or injury, as elucidated by Cannon,[4] which consists in the release of epinephrine from the adrenal glands as a result of sympathetic-nerve stimulation. This in turn brings about a glycolytic release of blood sugar from the liver, resulting in temporary hyperglycemia. This mobilization of blood sugar in the case of tobacco smoking, which may be detected within a few minutes following the beginning of smoking (Haggard and Greenberg[5]) is then a protective response of Nature, in which the body reserves are called upon to repel a toxic invasion of the organism, the surplus of blood sugar being utilized in the maintenance of tissue oxidation so essential to detoxication, as shown in a previous paper.[6] The visceral changes associated with this response are all capable of aiding in the protective action. These consist in the cessation or slowing of gastrointestinal motility and digestion, thus releasing energy for other needs; the shifting of blood from abdominal organs to organs immediately essential for muscular effort, as in increased heart action and respiration; the discharge of extra red-blood corpuscles and platelets from the spleen, thus increasing the oxygen-carrying capacity and coagulability of the blood as an emergency protection in possible hemorrhage. It is this last feature of this protective response—the increased coagulability of the blood—which, if often repeated as in smoking, may become pathogenic by favoring the development of thrombotic processes. The work of Josue[6A] gives support to this hypothesis. He found that small repeated doses of adrenalin, given intravenously to experimental animals every other day for several weeks or months, would produce multiple atheromatous lesions of the aorta similar to those found in man. The findings of De Takats[7] also seem significant in this respect. He presents data to show that various procedures and drugs which stimulate the autonomic nervous system shorten the blood-coagulation time, apparently through the mediation of the adrenal glands. A similar adrenal reaction occurs in post-operative conditions as a result of the traumatic shock, the associated loss of blood, and the toxic anoxic effect of the anesthetic, and might thus account for the incidence of post-

operative thrombosis. Recently Ochsner et al[8] have brought forward considerable evidence to indicate that the rising incidence of post-operative thrombosis may be due in part to the prevalent use of antibiotics, since all of these have been found to increase the blood-coagulation rate. The protective sympatheticoadrenal response to toxic invasion may here also prove to be a factor.

There is still another approach to this problem,—the indirect effect of tobacco and narcotics in general upon the nutritional status, particularly the vitamin reserve, and the possible influence of such effect upon the development of thrombosis. Quastel and Wheatley[9] have shown that narcotics (which would include tobacco and alcohol) greatly increase the bodily requirement of vitamin B_1, thus increasing tendency to deficiency of same. The tissue concentration of vitamin C is also known to be rapidly depleted in toxic conditions, endogenous or exogenous. When thus utilized less of the vitamin remains for physiological needs, thus accentuating the morbific effect. (To illustrate, I have found in clinical research that the smoking of one cigarette increases the bodily requirement of vitamin C by 25 mg., or the vitamin-C content of one orange, thus precluding the likelihood of any heavy smoker ever attaining an optimal tissue level of this vitamin.) Recently Paterson[10] has called attention to the low vitamin-C status of coronary thrombosis cases. He found that 81 per cent of such cases in hospital practice had a subnormal blood-plasma level as compared to 55.8 per cent in a corresponding group of general public-ward patients. He attributes the precipitation of thrombosis to a prior subintimal capillary hemorrhage at the site of the lesion, which he has verified at autopsy. He regards this hemorrhagic prelude as due to C-avitaminosis and suggests that patients with this disease be assured of an adequate intake of this vitamin.

A brief survey of the physiological effects of deficiency of vitamins B_1 and C may clarify the pathological mechanism leading to thrombosis and occlusion of blood vessels. An outstanding feature of B_1-hypovitaminosis is the tendency to hypotonicity of all non-striated muscle tissue, which would include the musculature of the coronary arteries. This hypotonia results in vascular dilatation and consequent slowing of blood movement, even to stasis in the capilliaries at times. Furthermore, the lack of the catalytic action of this vitamin results in an undue accumulation of the carbohydrate metabolites, notably lactic acid, pyruvic acid and carbon dioxide. As these reach a higher level of concentration in the blood the oxygen uptake in the tissues is lowered, and the subject suffers from increasing fatigability, shortness of breath, drowsiness, cyanosis and other signs of anoxemia. While these are characteristic signs of B_1-hypovitaminosis they are also often premonitory signs of coronary and myocardial insufficiency. Gaskell[11] and Langley[12] find that increase in blood-lactic acid level produces vasodilatation, while Shepard[13] claims that increased carbon dioxide produces cellular swelling, resulting in an increase in the volume of individual red-blood corpuscles and consequently a retarding of the capillary blood velocity. He believes these factors may be the determining events in the development of thrombosis. According to Findlay[14] the principal effect of C-hypovitaminosis is the tendecy to capillary fragility, resulting in edema and petechial hemorrhage due to weakening and swelling of the endothelial walls, which is associated with damage of the intercellular cement substance. This causes retardation of blood flow and passive congestion, resulting in deficient oxygenation of the tissues, all of which favor thrombotic development. A correlation of these observations points significantly to the possible pathogenic sequences of tobacco and alcohol addiction and consequent vitamin deficiency as related to coronary thrombogenesis.

The discussion of this subject would be incomplete without reference to the recently advanced theory of cholesterol relationship. While it must be admitted that a high blood-cholesterol level is generally associated with atherosclerosis and thrombosis, there is much evidence to indicate that disturbances in endogenous synthesis and metabolism may be more responsible than excessive ingestion of this substance, since attempts to lower the blood-cholesterol by restricting cholesterol intake have not been very successful. Biskind[15] claims that deprivation of the B and C vitamins, or their depletion in liver detoxication of exogenous poisons, may result in liver damage and loss of ability to metabolize cholesterol with consequent high blood levels of same. He states that patients so afflicted are usually advised not to eat liver, eggs and other cholesterol-rich foods, and that this interdiction further impairs nutritional status. "When these patients are placed on a regime combining the available crystalline vitamins and dessicated or cooked whole liver there is usually a dramatic reduction in blood-cholesterol despite the greatly increased intake." The findings of Schlichter et al[16] also seem to indicate that a preconditioning factor in the affected blood vessel, involving injury to the local vasa vasorum such as that produced experimentally by cauterization, may precipitate cholesterol deposition at the site of such injury. This would give support to the afore-mentioned observation of Paterson[10] that thrombotic lesions were found to develop on the site of subintimal hemorrhages consequent to vitamin-C deficiency. Such hemorrhages would constitute an injury to the vasa vasorum, and since tobacco smoking is conducive to C-hypovitaminosis herein may lie the link in etiological relationship with thrombosis.

Relative to the predominant male-sex incidence of coronary thrombosis Levine[17] 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 disease in the male. One may ascribe it to the greater amount of work that men do, although some might question this and maintain that the humble housewife does just as much work in her home . . . Another factor that may be mentioned is the possible role of tobacco . . . Certainly the consumption of tobacco has been in the past almost entirely confined to men, and has been one of the few acquired differences in habit between the sexes. It is therefore logical to suspect this habit of playing some possible role in producing such a male preponderance in susceptibility to this disease. A more definite answer may be apparent before long if the coming generation of women continue the smoking habit that seems to have become so general." This forecast was made in 1929, and already the anticipated answer seems to be in evidence. Prior to 1929 the sex ratio of incidence of coronary thrombosis has been estimated as high as 5 males to 1 female. However, recent figures supplied by the Toronto Health Department indicate that the present sex ratio in this disease is 2 males to 1 female. Apparently the rising tide of tobacco addiction in women is exercising a leveling action

on the sex ratio of incidence of this form of heart disease.

It should further be noted that the rising incidence of coronary and other forms of thrombotic disease has been closely concurrent with the increase in tobacco consumption. Cigarette consumption in Canada has risen from approximately 5 billion in 1935 to 18 billion in 1951, an increase of over 350 per cent while in the same time the population has increased about 25 per cent. During this same period the incidence of coronary thrombosis, Buerger's disease and post-operative thrombosis has shown a closely proportionate increase. A closely parallel situation prevails in United States where the tobacco per-capita consumption is about double that of Canada. One thing is certain, there has been no such increase in the consumption of cholesterol-rich foods by the populace at large during this same period, as would be expected if the cholesterol-ingestion etiology is sustained. On the contrary, statistics indicate a noticeable drop in per-capita consumption of such foods (milk, butter, eggs and meat) during the period in question.

In recent years much stress has been given to the deleterious effects of involuntary inhalation of toxic elements in industrial smoke and fumes ("smog"), tetra-ethyl lead in gasoline, DDT, etc. These are all undoubtedly pathogenic, but with the redeeming feature that they are usually taken in a high degree of atmospheric dilution. On the contrary, little or no attention is given to the voluntary inhalation of toxic fumes in concentrated form in the smoking of over 400 billion cigarettes annually by the people of America. We "strain at a gnat and swallow a 'camel'."

SUMMARY

The rising incidence of heart disease, particularly coronary thrombosis, is discussed. The rapid increase in thrombotic disease is thought to be referable to metabolic disturbances brought about by deficiency of vitamins B1 and C associated with narcotic addiction, notably tobacco and alcohol, and to hepatoxic action by these same agents, resulting in conditions favorable to thrombosis, including hypercholesterolemia.

A report of findings in 151 male cases of coronary thrombosis shows the average age of death to be 52 years. Of these cases practically 100 per cent were found to have been tobacco addicts and 55 per cent also users of alcohol. In a similar-age group of non-thrombotic male patients (118 cases) the rates of tobacco and alcohol addiction were 66 per cent and 29 per cent respectively. The average age of the heavy smokers at death in the coronary-thrombosis group was 47 years, while that of the light and moderate smokers was 58¼ years.

The sex incidence of coronary thrombosis, which has been predominantly male,—5 to 1 and 3½ to 1 in earlier reports, has shown a trend toward a relative rise in female incidence, latest reports indicating a ratio of 2 males to 1 female. This change in sex incidence apparently reflects the influence of increasing female addiction to tobacco and alcohol. The rising incidence in general has closely paralleled the increased consumption of these narcotics. There has been no such parallel in the consumption of cholesterol-rich foods (milk, butter, eggs and meat). On the contrary, statistics indicate a marked drop in per-capita ingestion of such food products.

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