CORONARY THROMBOSIS : An Etiological Study

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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 disease pre-eminently in the lead—a greater cause of death than cancer, tuberculosis and diabetes combined. So rapidly indeed has the incidence of coronary thrombosis risen in recent years that it is now the principal cause of death for all past fifty years of age. (See Chart No. 1.)

Deaths from heart disease, at five year intervals, as reported in Canada, were as follows: 6,021 in 1921; 11,793 in 1926; 13,734 in 1931; 16,424 in 1936; and 26,602 in 1941.* In the last three years there has been a further increase of approximately 15%, assuming that the figures for Canada as a whole are proportionate to those of the city of Toronto. (See Table No.1.)

Deaths from heart disease in the city of Toronto during the past eight years were as follows: 1,574 in 1937; 1,623 in 1938; 1,771 in 1939; 1,929 in 1940; 2,538 in 1941;* 2,648 in 1942; 2,790 in 1943; and 2,734 in 1944.

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 the incidence of coronary disease (see Table No. 2), 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.

*NOTE: A disproportionate increase will be noted in 1941, due to certain changes in the coding classification of the causes of death. There have been no changes in this respect since 1941.

CHART No. 1

Deaths from Heart Disease in Canada

In all Canada		*In the City of Toronto*			
Year	*Total*	*Year*	*Total*	*Male*	*Female*
1921	6,021	1937	1,574	929	645
1926	11,793	1938	1,623	934	689
1931	13,734	1939	1,771	1,031	740
1936	16,424	1940	1,929	1,151	778
1941*	26,602	1941*	2,538	1,396	1,142
—	——	1942	2,648	1,466	1,182
—	——	1943	2,790	1,510	1,280

CHART No. 2

Causes of Death among American Physicians

Year	*Total Deaths*	*Cardiac Deaths*	*% of Total*	*Coronary Deaths*	*% of Total*
1933	3,354	1,131	33%	107	3%
1934	3,393	1,351	38%	256	7½%
1935	3,491	1,343	38%	366	10½%
1936	3,581	1,374	38%	318	9%
1937	3,398	1,358	37%	387	10%
1938	3,768	1,491	39%	588	15%
1939	3,879	1,583	40%	676	17%
1940	3,633	1,515	41%	691	19%

CHART No. 3

Data re 269 Male Deaths in the Toronto District — 1941 to 1944

Disease Group	*Cases*	*Age*	*Height*	*Wt.*	*% Using Tobacco*	*% Using Alcohol*
Coronary Thrombosis	151	52	5′ 8″	168	94%	55%
Coronary Sclerosis	23	69	5′ 9″	159½	52%	13%
Non-coronary Heart	22	61	5′ 8½″	168	77%	23%
Cerebral hemorrhage	16	61	5′ 8″	166	50%	31%
Cancer	18	53	5′ 9″	166	88%	50%
Miscellaneous	39	58	5′ 9″	161	64%	28%

CHART No. 4

Death Rates per 100,000 in U. S. A.

Year	*Heart Disease in whole country*	*In the State of Massachusetts*			
		Heart	*Cancer*	*T. B.*	*Pneumonia*
1900	137.4	—	—	—	—
1910	158.9	131	90	182	110
1920	159.6	178	116	118	74
1930	214.2	267	137	64	44
1940	292.5	422	167	37	21

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 incidence, 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. (Forty years ago the famous Osler referred to pneumonia as the old people's friend.) Neither does it explain the rising female incidence of heart disease relative to the male incidence, which will be referred to later. (3) While it is true that the average span of life has been practically doubled in the last forty years, this has been accomplished mainly by reduction in infant and child mortality as a result of better control of infectious diseases and improved nutrition. Unfortunately, however, adult nutrition has not been materially improved, and the toll of the degenerative diseases of middle life has not been reduced or postponed. Accordingly, post-65 life expectancy has only slightly increased. In 1900 life expectancy for males at 65 years was 76.4, whereas at present it is 76.9 years. (4) The rate of increase in

heart disease, particularly coronary thrombosis, has been disproportionately greater than the rate of aging of our population.

A glance at Chart No. 2, showing the relative percentage of cardiac and coronary deaths in American physicians from 1933 to 1940 inclusive, indicates a rise in incidence of cardiac deaths from 33% to 41% of total deaths, whereas the coronary deaths show a rise from 3% to 19% of total deaths. Obviously the aging of the medical profession in this short period could not possibly account for such an increase, particularly the relative increase in coronary deaths. Neither is it reasonable to believe that improved methods of 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 over thirty years, and physicians as a rule have consultation 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 years ago Aikman [1] sounded a note of alarm in these words: "It is a well known fact that diseases of the heart and vascular system 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 determine the nature of this insidious etiological factor I have conducted, during the past three years, a survey by means of a questionnaire mailed to the widows or next of kin of middle-aged males who have died suddenly in the Toronto district, assuming that many 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, including 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 were grouped as follows: Coronary sclerosis (angina pectoris) —23 cases; non-coronary cardiac disease (valvular and other types)—22 cases; cerebral hemorrhage —16 cases; cancer—18 cases; and miscellaneous (pneumonia, anemia, nephritis, diabetes, etc.)—39 cases.

In the coronary thrombosis group (151 cases) the average age at death was found to be 52 years; the average height was 5′ 8″; and the average weight was 168 lbs. Sixteen were 200 lbs. and over, one being 295 lbs. One hundred and forty-two (94%) were tobacco smokers, 59 being light or moderate smokers and 83 heavy smokers, and nine (6%) were non-smokers. (It is more than likely that an even higher percentage of these cases actually were or had been smokers, since a second check on a number of them elicited the fact that they had discontinued smoking a month or so before death, either on their own volition or under medical advice.) There were 82 (55%) users of alcohol and 69 (45%) non-alcoholics. The average age of the smokers at death was 52 years,—the non-smokers 59½ years. The average age of the heavy smokers at death was 47 years,—the light and moderate smokers 58½ years. The average age of the alcoholics at death was 47½ years,—the non-alcoholics 58 years. In this group 30 cases died at 50 years and under, 13 at 45 years and under, 6 at 40 years and under, 2 at 35 years and under, and 2 under 30 years. The two youngest, 27 and 29 years, were heavy users of tobacco and were alcoholics as well.

In the coronary sclerosis group (23 cases) the average age at death was 69 years and 4 months. The average height was 5′ 9″, and the average weight was 159½ lbs. In this group 12 (52%) were tobacco users, and 3 (13%) were also users of alcohol.

In the non-coronary cardiac group (22 cases) the average age at death was 61 years. The average height was 5′ 8½″, and the average weight was 168 lbs. There were 17 (77%) tobacco smokers in this group, and 5 (23%) were also alcoholics.

In the cerebral-hemorrhage group (16 cases) the

average age at death was 61 years. The average height was 5′ 8″, and the average weight was 166 lbs. There were 8 (50%) tobacco smokers in this group, 5 (31%) being also alcoholics.

In the cancer group (18 cases) the average age at death was 53½ years. The average height was 5′ 9″, and the average weight was 166 lbs. There were 16 (88%) tobacco smokers in this group, 9 (50%) being also alcoholics.

In the miscellaneous group (39 cases) the average age at death was 58 years. The average height was 5′ 9″, and the average weight was 161 lbs. In this group there were 25 (64%) tobacco smokers, 11 (28%) being also alcoholics.

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

Regarding exercise, most of the coronary-thrombosis group were reported as physically active, not a few being athletically inclined (golf, badminton, etc.) until such time as the onset of their illness curtailed their activities.

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% and 55% respectively, as compared to the combined non-coronary-thrombosis groups, 66% and 29% respectively. The coronary sclerosis group provided the most marked comparative difference in this respect, the tobacco smokers being only 52% and the alcoholics 13%. The age span of this latter group, averaging 69 years, as compared to that of the coronary-thrombosis group, 52 years, is also strikingly significant.

The break-down of the age figures in the coronary-thrombosis group also provides evidence of the precip-

itating 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 addicted to tobacco only, and 59½ years for those not addicted to either.

The most striking feature in the figures for all the groups is the definite correlation of the life span and the degree of tobacco and alcohol addiction, the heavier addiction in the coronary-thrombosis and cancer groups being associated with a corresponding drop in the average age at death. In this respect it is interesting to note that the coronary-sclerosis group, with the lowest degree of combined tobacco and alcohol addiction, had the greatest average age at death—69 years and 4 months. It is also interesting to note an apparent correlation between the weight levels and the average age spans in the different groups, the lower weights generally having the longer life spans. (See Table No. 3.)

The height and weight ratios in the coronary groups seems also to be indicative of some nutritional relationship, the figures being 68 inches and 168 lbs. in the thrombosis group as compared to 69 inches and 159½ lbs. in the sclerosis group, suggesting the likelihood of a higher carbohydrate intake in the former. The findings of 16 cases in this group weighing 200 lbs. or over is significant in this respect.

A correlated study of other thrombotic disease processes may help to clarify the possible etiological rôle of tobacco and alcohol. 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 instances 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 etiological relationship between coronary

thrombosis and thromboangiitis obliterans is shown by the closely parallel features in their symptomatology and pathology, as follows: (1) The greater susceptibility of the male; (2) The pre-senile age group; (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 the latter in the vasa vasorum, and leading to progressive impairment in the structure and function of the musculature proper; while in the former (coronary thrombosis) the initial changes occur in the coronary blood vessels, 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 thromboangiitis obliterans, 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."

An explanation of the precipitating rôle 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, as shown by 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 calculated to aid 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 findings of De Takats[7] also seem significant in this respect. He reports on the effect of autonomic nervous stimuli on the clotting mechanism and 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 postoperative conditions as a result of the traumatic shock, the associated loss of blood, and the toxic anoxic effect of the anæsthetic, and might thus account for the incidence of thrombosis following surgical procedures.

There is still another angle of 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 on the pathological process of thrombosis. Quastel and Wheatley[8] have shown that narcotics greatly increase the requirement of vitamin B_1 in the body, so much so that even moderate doses of analgesic and hypnotic drugs are found to increase such requirement by as much as 40%. The tissue concentration of vitamin C is also known to be rapidly depleted in toxic conditions. In fact this vitamin is sometimes referred to as the

"antitoxic" vitamin. Holmes et al [9] have shown that vitamin C is more effective in lead poisoning than is the usual therapy with calcium. They point out that painters do not develop lead poisoning if their vitamin-C status is at high level. Personally I have found that preliminary or concurrent administration of large doses of vitamin C in sulfonamide therapy acts as a preventive of toxic reactions.[10] The ascorbic acid acts as a detoxifying agent, leaving less of the vitamin available for physiological purposes. In this way all toxic substances entering the body, which would include tobacco smoke,* tend to deplete the body reserves of vitamins B_1 and C; and, conversely, the depletion of these vitamins accentuates the morbific effect of all such toxic substances. Thus a vicious circle is established favoring pathogenesis. Recently Paterson [11] has called attention to the low vitamin-C status of coronary thrombosis cases. He found that 81% of such cases in hospital practice had a subnormal blood-plasma level of vitamin C, as compared to 55.8% deficient in a corresponding group of general public-ward patients. He attributes the precipitation of thrombosis to subintimal capillary hemorrhage resulting from capillary fragility associated with C avitaminosis, and recommends that patients with this disease be assured of an adequate intake of vitamin C.

A brief survey of the physiological effects of deficiency of vitamins B_1 and C may provide the clue to the pathological sequences leading to vascular thrombosis and occlusion. An outstanding feature of B_1 hypovitaminosis is the tendency to hypotonicity of all nonstriated muscle tissue, which would include the musculature of the coronary blood vessels. This vascular hypotonia tends particularly to venous dilatation and consequent slowing of blood movement, approximating stasis in the small capillaries. The lack of the catalytic action of vitamin B_1 results in an undue accumulation of the carbohydrate metabolites, notably lactic acid,

*NOTE: The smoke of a cigarette is known to contain the following: nicotine, carbon monoxide, hydrogen sulphide, wood alcohol, methylamine, ammonia, formaldehyde, methane, pyridine, furfurol, carbolic acid, prussic acid, arsenic and lead.

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 frequently the first signs of coronary and myocardial insufficiency. Gaskell [12] and Langley [13] find that increased lactic acid concentration produces vasodilatation, while Shepard [14] 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. These factors, he believes, may be the determining events in the production of thrombosis. According to Findlay [15] the principal physiological effect of C hypovitaminosis is the tendency 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. The endothelial swelling 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 smoking and vitamin deficiency as related to coronary thrombosis.

Relative to the predominant male sex incidence of coronary thrombosis Levine [16] says: "The sex distribution of this disease is most striking—a ratio of three and one-half males to one 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 rôle 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 rôle 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 incidence of coronary thrombosis has been estimated to be 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 two males to one female, the deaths recorded in this city for 1943 being 668 males and 334 females. Apparently the rising tide of tobacco addiction in women is exercising a leveling action on the sex incidence of this form of heart disease.

Allergy to tobacco may explain why some are more susceptible to its pathogenic effects than others. Green [17] has recently reported results of tobacco skin tests for sensitivity in 18 cases of coronary thrombosis and controls, indicating a ratio of 4.5 to 1 reacting positively as compared with the normal controls, despite the fact that the control age group was younger. A relatively higher ratio of sensitivity has been found in thromboangiitis obliterans also.

The correlation of anginal attacks and smoking has been repeatedly noted in the literature. Coronary insufficiency cases frequently report the exacerbation of precordial pain or angina of effort immediately following smoking, and not infrequently on their own initiative they reduce their smoking accordingly. Baltzan [18] has found this coincidence to be a dependable diagnostic sign in coronary disease.

As further evidence of this interrelationship it should be noted that the rising incidence of heart disease, particularly coronary thrombosis, has been closely concurrent with the increase in tobacco consumption. The cigarette consumption in Canada has risen from approximately 5 billion in 1935 to over 10 billion in 1943. The 1944 consumption is likely to exceed 11 billion. During this same period the incidence of heart disease has proportionately increased. A very similar parallel

prevails in the United States where tobacco consumption and heart disease incidence are at still higher levels. The cigarette consumption in the United States has risen from approximately 135 billion in 1935 to an estimated consumption of 333 billion in 1944; yet even at these stupendous figures there was an acute shortage of cigarettes before the year had ended. During this period heart disease, particularly in the eastern States, has taken a closely proportionate toll. (See Table No. 4.)

Confirmatory evidence of the intermediary rôle of vitamin deficiency in the pathogenesis of coronary disease has been found in the clinical treatment of incipient cases of the disease by administration of large doses of vitamins B_1 and C. In a considerable number of cases in which the premonitory symptoms—tachycardia, arrythmia, dyspnœa and angina of effort—were much in evidence I have obtained marked improvement, with relief of these symptoms, by this means. Such measures are, of course, ineffectual in the final stages when irreparable damage has been effected.

Summary

The rising incidence of heart disease, particularly coronary thrombosis, is discussed. The rapid increase in the incidence of thrombotic disease, affecting the presenile age group, is thought to be referable to metabolic disturbances brought about by deficiency of vitamins B_1 and C, accentuated by the sympathetico-adrenal response to narcotic addiction, notably tobacco and alcohol.

A report of findings in 151 male cases of coronary thrombosis, obtained by questionnaire from their widows, shows the average age at death to be 52 years. Of these cases 94% were found to have been tobacco addicts, and 55% were also users of alcoholic beverages. The average age of the heavy smokers at death was 47 years, while that of the non-smokers was 59½ 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 cannot be explained by improved diagnostic methods or relative aging of our female population, but apparently reflects the influence of increasing female addiction to tobacco and alcohol.

The clinical application of intensive vitamin B_1 and C therapy in a considerable number of incipient coronary cases has brought about marked improvement in all prodromal symptoms, and is thus confirmative of the author's concept of the etiological relationship of deficiency of these vitamins as accentuated by tobacco and alcohol addiction.

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