Editorial

Atherosclerosis of Cerebral Arteries in Japanese

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In mortality statistics (1964), it was reported that the death rate from cerebrovascular disease was 171 per 100,000 population in Japan and 106 in U.S.A. and yet the death rate of arteriosclerotic and degenerative heart disease was 51 and 319 respectively. From a recent satisfactory prospective population survey on cerebrovascular disease conducted by Katsuki, it has become clear that cerebral thrombosis is equally as important as cerebral hemorrhage among Japanese and the incidence of cerebral thrombosis is much higher than that of cerebral hemorrhage. Considering that the cerebral thrombosis and the coronary heart disease may develop on the basis of atherosclerosis or arteriosclerosis of these arteries, it is a great puzzle, why in Japanese the incidence of cerebral thrombosis is higher and yet the incidence of coronary heart disease is lower than those in Europeans and Americans. It is a current fashion to treat atherosclerosis as a disease of lipid metabolism, particularly of cholesterol or of the manner of its transport. Yet the serum cholesterol must be the same in the heart and in the head. Certainly this puzzle may not be solved only by studying the plasma lipids. To solve this puzzle, it will be valuable to investigate the severity of atherosclerosis of aorta, coronary and cerebral arteries among Japanese population and compare them with those reported on Americans, Europeans and other populations. And also studies on metabolism of arteries and mechanical factors as localizing factors in atherosclerosis will be valuable too.

There is a considerable number of papers reporting on the lesser incidence and severity of coronary atherosclerosis as well as aortic atherosclerosis in Japanese as evidenced in pathological and clinical findings. However, there is very few studies on the geographic pathology of cerebral atherosclerosis or arteriosclerosis in Japanese. Pathologically, it was emphasized that the arteriosclerotic lesions in cerebral arteries consist mainly of intimal fibrous thickening, reduplication and an increase of elastic tissues, but in aorta and most of the elastic arteries the atheromatous, necrotic lesions as well as plaque are the
main lesions. Generally, the reproducibility of the macroscopical grading methods for the evaluation of atherosclerosis is rather poor. In order to evaluate the patho-anatomical methods and results which were widely used nowadays for this purpose, such as Gore's and Baker's methods, chemical analyses of various arteries will be valuable, especially when applied in different countries by different researchers. Information of chemical compositions of cerebral artery, which is the most important artery in terms of cause of death, is practically lacking. We previously reported that the total cholesterol contents of Japanese cerebral arteries, obtained from the accidental death-case, were approximately the same up to 5th decade and significantly higher after the 8th decade of life than those of Americans and Europeans. Further studies, particularly on minerals and fibrous components of cerebral arteries are required to reach a final conclusion, whether the severity of atherosclerosis of Japanese cerebral arteries is greater than that in Americans or Europeans. However, the total cholesterol contents as well as severity of atherosclerosis of aorta and coronary artery were significantly lower than those of Americans and Europeans. Through personal communication with Dr. S. Katsuki, I have become aware that Katsuki's and Baker's group conducted the joint study and evaluated the severity and extent of cerebral atherosclerosis of approximately 5,000 Minnesota Americans and 1,000 Japanese (hospital-death-case) by Baker's method. They have demonstrated that there appears a possible ethnic difference in severity of cerebral atherosclerosis between Japanese and Minnesota populations, in the direction of greater involvement in the Japanese case. How should this puzzle be explained? The absence of a logical explanation for the lack of harmony between severity of atherosclerosis and its complications in the aorta, coronary and cerebral arteries among different countries and races, may suggest the necessity to study the local vascular factors as a possible contributory cause.

Clinically, it is all but accepted in every country that hypertension is closely related to certain forms, at least, of cerebrovascular disease. Since Anitschkow found a higher incidence of atherosclerosis in hypertensive than in normotensive individuals, the numerous results of other investigators are in keeping with this. However, there are variations in the findings, with regard to the sex and age, in which the effect of hypertension is most pronounced and to the location of artery such as aorta, coronary and cerebral arteries. Experimental evidence in various animals clearly elucidated the accelerating effects of hypertension on atherosclerosis, but most of the experimental studies on the effect of hypertension on atherosclerosis have been conducted with aortas and their main branches and very few on cerebral artery. As pointed out by Giertsen any conclusion from a study of one artery is not valid for another
artery without reservation and the disproportionate effect of hypertension in aorta, coronary and cerebral arteries was shown. Davis and Klainer, in 1940, studied the incidence of coronary sclerosis among Americans with and without hypertension and concluded that subjects with hypertension showed more coronary sclerosis than those without hypertension and that this difference was more marked among the young than the old but they concluded also that hypertension per se did not appear to be a prime factor in determination of degree of coronary sclerosis. A number of convincing prospective studies on the accelerating effects of hypertension have been conducted. If we look specifically at the relationship between hypertension and ischemic brain disease; we found fewer studies, but probably an even closer correlation. Young et al., in 1960, showed that the strength of the relationship of blood pressure to the degree of atherosclerosis is much greater for the cerebral arterial bed than for the coronary arterial bed. In 1964, Ikeda et al. studied the atherosclerosis of cerebral and coronary arteries of Japanese, not from the point of view of geographic comparison but by using subjects above 60 years of age who died at the old folks home. They concluded that atherosclerosis or arteriosclerosis of cerebral artery related to the levels of diastolic blood pressure but that of coronary artery related to the levels of serum cholesterol concentration, and that of cerebral artery did not. Pathologically, it is convinced that the arterial lesion which closely relates to the presence of hypertension, is not atherosclerosis of large artery but arteriosclerosis of arterioles or small arteries. There are but a few reports concerning morphological changes caused by experimental hypertension in the aorta and large cerebral arteries of the animals. In many instances, the records concentrated mainly on renal arteries, arterioles, and mesenteric or other small arteries but the aorta and large cerebral artery were not even mentioned. In 1957, Magarey reported that hyalinization, vacuolation and necrosis of aortic intima were a common feature in hypertensive rats. However, a few biochemical studies could show changes of metabolism of arterial tissues of hypertensive animal. Namely, Tobian et al. showed an increase of Na contents in aortas of hypertensive rats, and Crane histochemically demonstrated an increase of incorporation of $^{35}$S$_4$ into the lesion of small artery and of coronary artery. Manley demonstrated the increase of the ratio of chondroitin sulfate/hyaluronic acid in arteries in which blood pressure was high. Deming et al., in 1965, demonstrated that hypertension increases the rate of synthesis of cholesterol from acetate-C in the aortas and the liver. But these studies did not mention about cerebral arteries. Previously we found the significantly lower contents of acid mucopoly-saccharide compositions, such as uronic acid, hexosamine and acid hydrolysable sulfate, the lower percentage of esterification of cholesterol and the low value of c/p ratio
in the grossly normal cerebral arteries and the high contents of total glycerol in normal coronary arteries when compared with those in the grossly normal aortas, common carotid and renal arteries. In cerebral artery, the contents of hexosamine and uronic acid increased with an advancement of atherosclerosis paralleling an increase of arterial systolic and diastolic pressure levels. This did not occur in the other arteries, except that hexosamine contents of renal arteries increased with an increase of systolic blood pressure.

Previously we demonstrated that the contents of triglyceride, adenosine diphosphate (ADP), DNA and the respiratory activity of coronary arteries were twice those of aortas per unit of tissue weight.\textsuperscript{14} Nakatani et al.\textsuperscript{15} demonstrated that the rate of P\textsuperscript{32} incorporation into individual phospholipids of artery varied with animal species, location of arterial tree and age of animals. These findings may suggest the possibility of metabolic pattern differing in different arteries, particularly in the effects of hypertension and of hemodynamic factors or humoral factor, if any, as causes of development of atherosclerosis in a particular portion. Recently, we measured the contents of individual acid mucopolysaccharides of Japanese cerebral artery by use of column chromatography plus polyacetate electrophoresis and demonstrated the negligible amount of hyaluronic acid (HA) and lower content of chondroitin sulfate-C (CSA-C) in grossly normal cerebral arteries compared with those of our previous findings on Japanese aortas and coronary artery. The content of CSA-C increased and that of heparitin sulfate decreased with an advancement of atherosclerosis of cerebral arteries.\textsuperscript{3} The hyaluronic acid is considered to be related to elastic fibre.\textsuperscript{16} In cerebral artery, the development of media containing elastic fibre is poor and elastica externa was absent when compared with other arteries. The elastic tissues provide maintenance tension to hold the arterial wall against prevailing hydrostatic blood pressure without any continuous expenditure of energy. The relationship of the tension in vessels to elastica content of the vessel wall and the problems associated with the degeneration and of reduplication of elastica should be considered. Patchy distribution of the plaque in cerebral arteries induced the assumption that mechanical and hemodynamic factors might be an important local factor in atherosclerosis of cerebral artery. We selected three portions of Japanese cerebral arterial tree, such as the terminal portion of internal carotid artery, the beginning portion of anterior and posterior cerebral arteries and cut these arterial portions as a cross section. We evaluated the sites of predilection of plaque formation and found that more than 75\% of the all lesions were located at the sites of bifurcation and/or curvature on the inner aspects of all three arterial portions. At such sites, the tension is increased particularly by an increase of blood pressure. This result suggests the presence of significant
correlation between the site of atherosclerotic lesions and the sites of hydrostatic pressure and increased tensions (Laplace's law)\(^{17}\) or boundary layer separation in cerebral arteries.\(^{18},^{19}\)

The origin of lipids in atherosclerotic lesions has given rise to much controversy, speculation and hypothesis, i.e., abnormal filtration of low density plasma lipoprotein, alterations in the permeability of endothelium, basement membrane and ground substance, metabolic or structural faults, ischemic metabolic damage, essential fatty acid-deficiency, lipoprotein instability, and the increase of endogenous lipid synthesis within the arterial wall. Atherosclerotic lesion could be considered to be basically a local reaction of components of arterial wall to influences which upset the balance between functional demand and the functional capacity of the vessel to fill the demand. As arteries have their own metabolic personalities depending on their location, age and sex, and their characteristic susceptibility to atherosclerosis, the effects of various factors on atherosclerosis of coronary and cerebral arteries will be different each other. However, the logical explanation for the different susceptibility to atherosclerosis has not yet been obtained. Further studies on arterial diseases of cerebral artery are particularly required.

**References**