HISTORICAL VIGNETTE

ANITSCHKOW and IGNATOWSKI: Pioneers of Experimental Atherosclerosis Research

Descriptions of human atherosclerosis have been documented for centuries dating back to the Renaissance. In the nineteenth century, Carl von Rokitansky and Rudolph Virchow put forward concepts of the development of human atherosclerosis by, respectively, emphasizing encrustation of blood products onto the luminal surface and insudation of blood proteins into the arterial wall. While the basis for the development of atherosclerotic lesions had theoretical interest, the disease generally was regarded as an inevitable consequence of aging. In this milieu, experimental research into the pathogenesis of atherosclerosis began at the Imperial Military Medical Academy in St. Petersburg, Russia (1,2). Following graduation from medical school, Alexander I. Igantowski became involved in experimental work in the laboratory of the Nobel Prize-winning physiologist, Ivan P. Pavlov, in St. Petersburg. In 1908, Ignatowski reported that rabbits fed a diet of full-fat milk, eggs and meat soon developed pronounced atherosclerosis of the aorta (2). In 1913, Nikolai N. Anitschkow reported his experiments that showed that the key component in the experimental diet was cholesterol and that rabbits fed a diet with only high-cholesterol developed greatly elevated blood cholesterol levels and atheromatous lesions (1). Ignatowski subsequently moved to Yugoslavia after the Russian revolution and redirected his professional career to become a leader in academic internal medicine. Antischkow continued to refine the lipid hypothesis during a distinguished career as an experimental pathologist.

Anitschkow's observations and concepts initially received little recognition and application for a number of reasons (1). One reason was the view that the rabbit had an atypical response to dietary cholesterol compared to other animal models that did not develop vascular lesions on high fat diets; this was understandable given that information only subsequently became available about differences in metabolic responses affecting blood cholesterol levels of various species. A second and probably more significant reason was the rather fatalistic view that human atherosclerosis was an inevitable consequence of aging, not subject to modification. Building the case for the importance of hypercholesterolemia in human atherosclerosis was an uphill struggle. It was not until 1984, nearly 60 years after Anitschkow's initial reports, that the National Heart Institute completed the landmark 7-year Coronary Primary Prevention Trial, the first large-scale, randomized, double-blinded clinical trial showing that lowering blood cholesterol significantly lowered the risk of developing a myocardial infarction (1).

During the same 50-60 year interval, experimental studies of atherosclerosis continued and culminated with the formulation of the response to injury theory by Russell Ross and colleagues (3-5). This paradigm holds that atherosclerosis develops as a response of the vessel wall to chronic, repetitive injury leading to endothelial dysfunction, proliferation of vascular smooth muscle cells, influx of macrophages, intracellular and extracellular accumulation of cholesterol-rich lipid derived primarily from plasma low density lipoprotein, and deposition of collagenous matrix produced by the vascular smooth muscle cells in the growing atherosclerotic plaques. This paradigm has informed and been supported by subsequent experimental work in the field (3,6). Inflammation and native immunity have been found to have important roles in atherogenesis such that atherosclerosis is now considered an inflammatory disease response of the vessel wall to injury (7,8).

Nevertheless, the magnitude and relative importance of the role of diet high in saturated fats and cholesterol in the progression of human atherosclerosis has been the subject of vigorous debate over the years. The significance of Anitschkow's observations in the rabbit model have been vigorously challenged on several bases, including that the lesions in the initial reports were more akin to foam cell-rich fatty streaks rather than human atherosclerotic plaques and that the lesions only developed with tremendously high blood cholesterol levels. The primacy of hemodynamic factors over lipid levels has been championed (9). Also, harkening back to Ignatowski, the importance of excess or abnormal dietary proteins and related abnormalities has also been advanced. Most recently, the protein theory has been based on observations of premature atherosclerosis in young individuals with inherited homocysteinuria and the epidemiological data implicating homocysteinemia as a risk factor (10).

However, Antinskow's own work over many years enforced his initial observations and concepts (1). This includes the documentation of lesions more akin to human atherosclerotic plaques in rabbit models with more prolonged feeding of moderate levels of cholesterol and in the Watanabe rabbit model of human familial hypercholesterolemia (1, 11-13). Anitschkow himself advanced the notion of multi-causality of atherogenesis by stating that relatively high blood cholesterol was necessary but not always sufficient to induce atheromatous disease (1). A book has been published, The Cholesterol Wars, that chronicles the history of the sometimes quite violent controversies that surrounded the lipid hypothesis and how it finally came to be generally accepted, although a few pockets of stout resistance remain (1). Nevertheless, the uptake into the vessel wall of low density lipoprotein (LDL) cholesterol in proportion to circulating blood lipid levels followed by local oxidation and cellular uptake of the LDL and accumulation of cholesterol-rich lipid in developing atherosclerotic lesions remains a central tenant of the response to injury theory (3-8). (A scientific theory is a systematic synthesis of fact-based principles involved in a natural phenomenon and not pure speculation.)

The understanding of the pathogenesis of atherosclerosis is often mentioned as one of the greatest discoveries of the 20th century (1,2). There is a strong case that Anitschkow's seminal observations and concepts regarding this major human disease should have resulted in the award of the Nobel Prize for Physiology or Medicine. As Steinberg has pointed out, the mitigating factor against Anitschkow's receipt of the Prize was timing (1). Anitschkow was born in 1885 and published his classic paper in 1913. General acceptance of the validity and importance of the lipid hypothesis of atherogenesis did not come until 1984. Today, it is fitting to celebrate the 100th anniversary of the seminal insight into human vascular disease of this brilliant experimental pathologist, Nikolai N. Anitschkow.

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