critical issues in clinical care

A Tale of Two Lipids*
Cholesterol and Eicosapentaenoic Acid

Mark D. Altschule, M.D.

Cholesterol was isolated a century ago, and a few years later, the German chemist Winterstein showed that exposure to air caused its rapid oxidation to a dozen or more substances, some of which today are known to be angiotoxic. Thus, studies of the effects of giving cholesterol could be considered valid only if the chemical was freshly prepared, a requirement that has been neglected in all but a few of the thousands of published experiments on the feeding of cholesterol to animals. In recent years, such experiments have become less popular. When Anitschkow, in 1913, reported that feeding cholesterol to rabbits led to the development of atherosclerosis in them, his announcement was accorded little importance, because he did not demonstrate that his cholesterol was pure, and, in any case, the normal diet of rabbits contained plant sterols but almost no cholesterol.

Anitschkow's study was repeated several decades later by Timothy Leary, a Boston pathologist, who afterwards made the following remarkable statement:

As far as anyone knows, no cholesterol is synthesized by the human body. All of the supply is ingested. The most urgent demands for it come at times of rapid cell formation. Egg yolk is intended for the embryo. Milk is intended for the infant. It is interesting to note that Wells, in his Outline of History, records that it was relatively late in the evolution of primitive man that he developed what Wells calls 'the rather unnatural use of animal's milk as food.' The high blood cholesterol found in pregnant women marks the mobilization of this substance for the needs of the fetus in utero. Man is the only animal that ingests eggs and milk throughout its lifetime. Man is also the only animal, as far as is known, which dies in early life from coronary sclerosis, and which acquires atherosclerosis almost universally in advanced life.

The statement was received with amazement and some derision. It contained a breathtaking number of errors of fact, but nevertheless, had a degree of folksy attractiveness, for it was evangelical in tone; it voiced criticism of civilization; it quoted a popular author; it praised or at least excused motherhood; and it implied a belief in the notion that you are what you eat.

The decades since that time have seen the expenditure of millions of dollars and thousands of man-hours of work in trying to establish a relation in man between coronary atherosclerosis and the dietary intake of cholesterol. As mentioned, most of the animal experiments are worthless. There is, however, a vast amount of epidemiologic data in man. There are impressive lists of epidemiologic papers, all imperfect, inconclusive, or definitely flawed in one way or another. A number of anomalous findings have been presented. Studies in seven countries show that expectations of coronary death in the United States and northern Europe far exceed those in southern Europe in relation to serum cholesterol level, as well as all other so-called risk factors. In several places, eg, Stockholm, the cholesterol factor was not found to be operative. In studies of women, this factor was of less importance than in men, and in men, it appeared to be statistically significant only before age 50. There is no relation between serum cholesterol level and the progression, or lack of it, of coronary atherosclerosis. Particularly interesting was the finding of a high frequency of coronary atherosclerosis and myocardial infarction among the first degree relatives of the wives of patients. It certainly appears that by specialized breeding, Nature is attempting to develop a variety of humans with a high incidence of coronary atherosclerosis.

Whoever is interested in the overall problem should avoid the polemics in literature and read Mitchell's restrained but forthright analysis, with its negative conclusions.

An interesting sidelong on the cholesterol problem is to be found in the writings of Phillips. After showing that serum cholesterol levels have little or nothing to do with coronary atherosclerosis, he analyzed the data on the role of hyperestrogenemia in the etiology of the disease and related the findings to the feminization of men by civilized living, a concept that would delight philosophers of classical Greece and Rome.

Compare the happenings in the field of cholesterol metabolism with those involving another lipid, eicosapentaenoic acid. The story begins with the finding that Greenland Eskimos have little coronary atherosclerosis. It is now evident that other fish-eating peoples fall into the same category. Cold water fish contain eicosapentaenoic acid, a platelet inhibitor, with somewhat less of it in warm-water fish. The substance has been isolated and is being studied in human disease. In the meantime, we should perhaps reflect with regret that a...
couple of generations ago, almost all American children and youths took large amounts of cod liver oil, whereas now, owing to advances in science, they are given pure vitamin D mostly in enriched milk, without the antiplatelet factor. Too much science? We must also reflect that when the Roman Catholic Church relaxed its rule on the eating of fish on Friday, it did the public health a disservice. Too much liberalizing of religious customs?

In any case, the contrast between the way the cholesterol problem and the fish oil problem is being handled is notable.

REFERENCES
3 Wei JY, Bulkey BH. Myocardial infarction before age 36 years in women: predominance of apparent nonatherosclerotic events. Am Heart J 1982; 104:561-66
6 ten Kate LP, Boman H, Daiger SP, Motulsky AG. Increased frequency of coronary heart disease in relatives of wives of myocardial infarction survivors: assortive mating for lifestyle and risk factors? Am J Cardiol 1984; 53:399-403

Some Neglected Aspects of Respiratory Function In Pleural Effusions

The Diaphragmatic Arch

Mark D. Altschule, M.D.*

Between breaths, the diaphragm, pulled up by the normal negative intrapleural pressure, assumes a domed shape. Its attachments are all peripheral. When the diaphragm contracts it becomes flat and loses its dome, thereby pulling in air through the nasopharynx and large airways. At the end of inspiration, it relaxes and, under the influence of the lung parenchyma, is pulled back into its domed shape. These changes are best seen in lateral roentgenographic views of the chest. Loss of the domed shape, owing to loss of pulmonary elasticity or any other factor, seriously impairs normal breathing and increases the activity of the other respiratory muscles.

The effects of pleural effusions depend not only on the amount of the fluid but also on the presence or absence of extensive pulmonary parenchymal lesions. Normally, the measurements of pulmonary function vary so much that defining the effects of hydrothorax is difficult. Physical and roentgenographic examination are both inaccurate since the amount of free fluid present is always larger than expected, unless the fluid is encapsulated. If a radiopaque liquid lipid substance is introduced into the pleural space it will float to the top, thereby defining the upper limit of the effusion. Studied in this way, the effusion is always higher than expected. Egophony is the most accurate physical sign of fluid level, but it is not always present. Mediastinal shift is an accurate roentgenographic sign of large pleural effusions, but is absent with smaller effusions.

A pleural effusion of moderate or large size causes an increase in peripheral venous pressure, but not necessarily above normal limits. This pre-cardiac phenomenon is not accompanied by a fall in cardiac output. The amount of rise of the latter during exercise may, however, be limited.

The effects of hydrothorax on respiratory function are usually surprisingly small, although the presence of the fluid causes atelectasis as revealed by a decrease in functional residual (subtidal) air volume in the lungs. This is unlikely to cause dyspnea or arterial hypoxemia at rest, but it may cause respiratory discomfort on exertion. The reason for the common absence of arterial hypoxemia at rest is well-known. Air in the lungs (functional residual air) is oxygenated by mixing with inspired air. The ratio of effective inspired air (tidal air minus dead-space volume × respiratory rate) to functional residual air must be 2:1 or higher to cause effective air mixture in the lungs and prevent arterial blood hypoxia. Accordingly when respiration is made shallow by the presence of an effusion, the simultaneous production of atelectasis keeps the ratio at about 2:1 so that mixing in the remaining functional lung is adequate. However, atelectasis limits the expansibility of the lungs and may produce dyspnea on exertion.

When thoracocentesis is performed, atelectasis is not immediately abolished; re-expansion may take as long as several weeks. The immediate effect of thoracocentesis is to restore the normal diaphragmatic arch, thereby making respiration more efficient despite the persistence of atelectasis. There may also be some decrease in venous pressure, followed by diuresis if peripheral edema is also present. It is a clinical fact that when a small pleural effusion causes dyspnea, and a small thoracocentesis (400 to 500 ml) gives relief, there must also be extensive parenchymal pulmonary disease.

REFERENCE