EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN DOGS

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In the experimental study of atherosclerosis during the past few decades, many experiments have been undertaken to produce atherosclerosis by N. N. Anichkov's method, by means of the prolonged feeding of cholesterol to rabbits and fowls. Recently experimental atherosclerosis has also been produced in dogs [1-8]. According to existing evidence, this last model resembles human atherosclerosis closest in the character and localization of the morphological changes in the cardiovascular system. In dogs, even in the earliest stages of development of cholesterol atherosclerosis, the coronary arteries of the heart and the vessels of the base of the brain are involved, i.e., those portions of the cardiovascular system which suffer most often in atherosclerosis in man.

The present work is devoted to the study of certain problems of the clinical physiology of atherosclerosis in experiments on dogs.

METHODS

Most authors [1-3, 5-8] have produced experimental atherosclerosis by the enteral administration to dogs of a solution of cholesterol in fat or ether, together with methylthiouracil. As a preliminary step, 2-3 months before receiving the cholesterol, the dogs were given methylthiouracil in order to suppress thyroid gland function and thereby to lower their basal metabolism, since otherwise atherosclerosis does not develop in dogs. The thyroidectomy which is sometimes performed for this purpose is not always effective, for dogs often have accessory lobes of the thyroid gland.

In our work we used T. A. Sinitsyna's method [4], by means of which marked atherosclerosis may be obtained in a shorter time and without the preliminary administration of methylthiouracil alone. To ten male dogs, 3-4 years old and weighing from 16 to 22 kg, we gave a 20% solution of cholesterol in sunflower oil enterally for 120 days in a daily dose of 1 g cholesterol per kg body weight. Simultaneously with the cholesterol, for 60 days the dogs were given 1.5 g and, for the next 60 days, 1.0 g of 6-methylthiouracil. After the administration of cholesterol and of 6-methylthiouracil had been discontinued, the animals remained under observation for not less than one month. Two dogs which received 1.5 g 6-methylthiouracil daily, enterally, for 90 days acted as controls. During the first 60 days the dogs received the cholesterol solution and the 6-methylthiouracil in 200 g of boiled, minced meat. At the end of this period the majority of animals began to refuse this mixture and we had to give the same doses of cholesterol and 6-methylthiouracil forcibly. The experimenter opened the dog's mouth and his assistant dropped the cholesterol solution inside, without the use of a tube, after which the weight sample of 6-methylthiouracil was introduced far back into the mouth and the animal was given meat.
RESULTS

A few weeks after the beginning of the experiment the dogs became lethargic and made no playful movements. Some dogs grew thin and weak, and it was necessary to reduce their dose of 6-methylthiouracil or to discontinue it completely for 7-14 days. In the dogs of the control group there were no pronounced signs of hypothyroidism. The weight of the animals changed appreciably. In five dogs it rose at the end of the experiment by 2-5 kg, and in dog No. 8 it rose by as much as 10 kg. In three animals at first it rose by 1-2 kg, and then, as signs of hypothyroidism developed, it fell to 1.5-4 kg below the initial weight. The control dogs gained 1-2 kg in weight. One month after the cessation of administration of cholesterol and 6-methylthiouracil, the weight of the experimental animals almost returned to its initial value. The overloading with exogeneous cholesterol in conjunction with 6-methylthiouracil evidently caused considerable disturbance of the metabolic processes of the animal, more so than the administration of 6-methylthiouracil alone.

The blood cholesterol concentration was determined regularly, not less often than once every 3 weeks, in all the animals by Grigaud's method. Blood for the determination was taken from a vein in the region of the springing joint, always before the dogs had taken food, cholesterol and 6-methylthiouracil. The initial concentration of cholesterol in the blood varied in the experimental animals from 120 to 160 mg%, and rose in the course of the experiment on the average six- or eight-fold. The maximum blood cholesterol concentration in one dog reached 1200 mg% (Fig. 1). In the control dogs the blood cholesterol increased by 50-100%. In Fig. 1 a fall may be seen in the alimentary hypercholesteremia, taking place in the majority of dogs after 2-3 months of continuous administration of cholesterol and 6-methylthiouracil. This fact is evidently associated with the mobilization of the defensive and compensatory mechanisms of the body.

In all the dogs in the period of preliminary investigation, under ether and chloroform anesthesia, we exteriorized the left common carotid artery in a skin flap for measurement of the blood pressure and registration of the pulse wave. We measured the maximum arterial pressure by a palpatory method using a small rubber cuff, connected to a sphygmomanometer. The blood pressure was measured regularly at the same time of morning in a conditioned reflex chamber, before and after physical exertion in each experiment. During this procedure the dogs lay quietly on the bench without being strapped. The measurements began 1-3 months before the beginning of the experiment and continued for not less than a month after cessation of feeding. The maximum arterial blood pressure varied quite sharply from experiment to experiment; no animal in either the experimental or control group showed a persistent increase in the pressure. The reaction of the blood pressure to moderate physical exertion (running on an electrical moving belt for 5 minutes, with the belt moving at a velocity of 6.5 km/hr)