Rapid Production of Atherosclerosis by Administration of Uranium in Presence of Hypercholesterolemia. (17819)

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The recent demonstration by Holman that arterial disease may develop rapidly in man (1) and that in animals renal damage under certain conditions may result in the abrupt occurrence of arterial lesions(2) emphasizes the importance of determining those factors which are necessary for the rapid production of arterial vascular disease. This study is concerned with the rapid development of atherosclerosis in animals with hypercholesterolemia following the production of renal damage by the administration of uranium.

Methods. Male, albino rabbits between 10 and 12 months of age from a single colony were used. Cholesterol was administered by dissolving 5 g of cholesterol in ether and mixing this with Purina rabbit chow. The ether was evaporated and rabbits paired in cages were fed cholesterol by this technic 3 times a week. No supplementary feedings of vegetable greens were provided during this experiment. Water was freely available. Total cholesterol determinations using the Liebermann-Burchard reaction were made on ear vein blood each week. Kidney damage was produced by the subcutaneous administration of uranium acetate in a 10 mg per kg dose. Non-protein nitrogen determinations were made before uranium administration and just prior to sacrifice in animals receiving this chemical. All animals were killed by nembutal administration at the conclusion of the experiment and the thoracic and abdominal aortas were removed and fixed in formalin. Staining of the entire aorta with Sudan IV and confirmation of the presence of atherosclerosis by microscopic examination was carried out. The degree of atherosclerosis in the aorta was arbitrarily graded in the Sudan stained gross preparations on a 1 plus to 4 plus scale. Gross and microscopic examinations of the liver and kidneys were made in all experimental animals.

Four groups of animals were studied: (a) 10 animals with each pair fed 5 g of cholesterol 3 times weekly. These animals were sacrificed at the end of 3 weeks; (b) 10 animals fed Purina rabbit chow without additional cholesterol to which uranium acetate 10 mg per kg was given 3 to 14 days before sacrifice; (c) 14 animals maintained on the cholesterol feeding regime for 2 weeks, then given uranium acetate in the same dose and sacrificed from 2 to 14 days later; (d) 10 control animals from the same colony fed Purina rabbit chow alone.

Results. The data obtained are summarized in Table I. It will be noted that none of the control animals fed Purina chow alone and only 2 of the 10 normally fed animals receiving uranium acetate demonstrated significant atherosclerosis. Of the cholesterol fed group while 3 rabbits had atherosclerotic lesions of the aorta, these were of minimal degree. In the animals with hypercholesterolemia and uranium acetate administration 2 failed to demonstrate atherosclerosis but in the majority of rabbits in this group atherosclerosis was marked. All the cholesterol fed animals had some degree of fatty infiltration of the liver whereas the non-cholesterol fed animals did not. The kidneys of all rabbits receiving uranium had damage especially of the proximal convoluted tubules and to a much lesser extent of the glomeruli.

Discussion. The data herein presented does not permit identification of the factors responsible for the accelerated cholesterol deposition in the aorta in the presence of uranium acetate poisoning. However, the demonstration of the abrupt development of atherosclerosis in animals with hypercholesterolemia after the production of renal dam-

1. Holman, R., *Fed. Proc.*, 1949, v7, 273.
2. Holman, R., *Am. J. Path.*, 1941, v17, 359.

TABLE I.
Summary of Data.

Diet	No. of animals	Avg initial wt, g	Initial avg total cholesterol mg/100 ml	Final avg total cholesterol mg/100 ml*	Avg N.P.N. mg/100 ml*	No. animals with aortic atheroma
Normal	10	2543	55 (29-80) §	—	20	0
Normal + uranium acetate 10 mg/kg†	10	2760	56 (35-84)	—	48	2 +1, +4
Cholesterol 3 wks	10	2968	59 (26-100)	1321 (647-1995)	—	3 all +1
Cholesterol 2 wks then uranium acetate 10 mg/kg‡	14	2647	44 (19-67)	499 (197-884)	118	12 Avg +2.6

* Determined just prior to sacrifice.
† From 3 to 14 days elapsed between uranium dose to sacrifice, avg 6.1 days.
‡ From 2 to 14 days elapsed between uranium dose to sacrifice, avg 5.9 days.
§ Numbers within parentheses indicate range.

age by this agent, further substantiates Holman's observation that "Arterial disease may be a matter of days not decades."(1)

Summary. Rabbits with dietary hypercholesterolemia of short duration develop aortic atherosclerosis abruptly after the production of renal damage by the administration of uranium acetate.

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Joint Action of Penicillin with Chloramphenicol on an Experimental Streptococcal Infection of Mice.* (17820)

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In the course of studies on the effects of antibiotics on enterococci it was observed that chloramphenicol interfered with the early bactericidal action of penicillin(1). In the presence of both penicillin and chloramphenicol the rate of bactericidal action was considerably slower than with penicillin alone. It was of interest to determine whether this apparent antagonism between two antibiotic agents is limited to an *in vitro* phenomenon or whether it could be demonstrated *in vivo*. Since enterococci are essentially nonpathogenic for small laboratory animals, a highly fatal infection with beta hemolytic streptococci was used in the present experiments.

Materials and methods. White Swiss mice weighing about 20 g, from a heterozygous stock, were used in all experiments. The infections were produced with a beta hemolytic, group A, type 3, streptococcus, strain C 203, kindly supplied by Dr. H. Eagle. The virulence of this organism was kept at high level by passage through mice once or twice weekly. Cultures were grown in 5% sheep blood broth at 37°C for 18 hours. The LD_{50} for intraperitoneal injection of mice consisted of 60-100 organisms contained in 0.2 ml of a 10^{-6} dilution of an 18 hour cul-

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1. Jawetz, E., Gunnison, J. B., and Coleman, V. R., *Science*, 1950, v111, 254.