Hormonal Influences on Epinephrine Induced Aortic Sclerosis. (19230)

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Josue(1) produced, experimentally, degenerative aortic lesions in rabbits as an effect of repeated epinephrine injections. Since this original observation, a voluminous literature on this subject has accumulated. An extensive summary of this work is presented by Hueper(2). The incidence of the production of aortic lesions varies from author to author, both in the number of animals which are affected and in the intensity of the sclerosis in an individual animal. This variation ranges from 16% up to 100%. Although many attempts have been made to influence the course of epinephrine-induced sclerosis, our survey of the literature does not reveal any report on the influence of thyroxin and desoxycorticosterone on this process. It is noted, however, that Lortat and Sabareanu(3) found that thyroidectomy prevents the epinephrine-induced sclerosis. Others, however, could not confirm this. Theoretically, it would be expected that thyroxin should enhance the sclerosis induced by epinephrine. This is based on the well known observation that the sensitivity of tissue to epinephrine is increased by thyroxin. Specifically, it has been shown that epinephrine elicits a much greater blood pressure rise in dogs fed with thyroxin as compared to the normal control dogs. This augmentation of epinephrine effect by thyroxin could not be demonstrated on the vessels of the isolated limbs of dogs by Mikulicich(4). Desoxycorticosterone is reported to produce a vasopressor action with a general blood pressure rise (5). In addition, Selye and Stone(6) found desoxycorticosterone in large repeated doses resulted in sclerotic changes in the arterioles of chicks and rats. Arteriosclerotic changes also have been obtained from repeated implantations of adrenal cortex(7).

Methods. Fifty-seven rabbits were used in our study. The different groups were injected daily with the following materials: (1) epinephrine, intravenously, 50 μg of freshly made solution per kg, 1:1000 U.S.P. ampule diluted with sterile 0.9% sodium chloride solution. Some of the animals were given 25 μg per kg for the first 2 days, as a precaution against initial fatality. (2) Thyroxin, subcutaneously, 0.25 mg per kg, prepared from a 1 mg per ml ampule or prepared from thyroxin crystals* in a sterile 0.9% sodium chloride solution containing 2 drops of 0.4% sodium hydroxide. (3) Desoxycorticosterone acetate (cortate†), subcutaneously, 0.5 mg per kg and 1.0 mg per kg, of a 5 mg per ml solution in sesame oil. (4) Combinations of these.

Results. Table I outlines the results obtained. Animals which died after the first to fifth injection of epinephrine are grouped as early deaths. These deaths occurred within one-half hour after the intravenous administration of epinephrine, in a typical epinephrine asphyxial death, several animals showing hemorrhagic foamy sputum; such early deaths are not included in the observations for sclerosis. The one early death in the thyroxin group was a markedly cachectic animal, the death apparently being due to cardiovascular failure. All of the animals treated with thyroxin showed a rapid loss of weight and pronounced tachycardia. Aortic sclerosis was considered slight if only a few small plaques were seen in the supravalvular or thoracic aorta. Sclerosis was considered medium when numerous plaques were seen along the entire course of the aorta, some of which were confluent, partly ulcerated, and/or calcified. Severe sclerosis was recorded when whole segments of the aorta were involved, including the lower abdominal aorta.

Epinephrine alone produced only slight or medium sclerosis. Thyroxin alone produced no sclerotic changes, in spite of general cachexia. A combination of thyroxin and epinephrine showed sclerotic changes in all 8

* Thyroxine kindly supplied by E. R. Squibb and Co.

† Cortate supplied through courtesy of Schering, Inc.

TABLE I. Aortic Sclerosis Associated with Hormone Injections.

Daily treatment	No. of rabbits	Early deaths	Gross aortic sclerosis				Later deaths	Sacrificed after 26 days
			None	Slight	Medium	Severe		
E* (50)	14	4	2	4	4	0	4	6
T† (.25)	5	1	4	0	0	0	2	2
E (50) T (.25)	14	6	0	1	3	4	8	0
E (50) DCA (.5)	2	0	2	0	0	0	0	2
E (75) DCA (.5)	2	0	1	0	1	0	0	2
E (50) DCA (1)	13	3	9	1	0	0	4	6
E (50) T (.25) DCA (1)	7	4	0	0	0	3	3	0
Totals	57	18	18	6	8	7	21	18

* Epinephrine (E): in μg per kilo, intravenously.
† Thyroxine (T), and desoxycorticosterone acetate (DCA): in mg per kilo, subcutaneously.

rabbits so injected, most of the animals demonstrating a more severe grade of aortic sclerosis than was seen in the epinephrine group. In some of the cases where the animals died after only five injections, this severe degree of sclerosis was already present. In the animals treated with epinephrine and desoxycorticosterone only a slight degree of sclerosis was observed in 2 out of 14 animals. In the rabbits treated with a combination of epinephrine, desoxycorticosterone, and thyroxin, all 3 of the 3 animals showed a severe degree of sclerosis, which occurred very early, as soon as 6 days after beginning the treatment.

Prominent changes were observed in the appearance of the lungs of the animals which died, during the first 4 days of treatment, immediately after epinephrine injection. The lungs of animals treated with thyroxin and epinephrine showed a marked pulmonary edema and were severely hemorrhagic, their appearance resembling the red hepatization of pneumonitis. Animals which received only epinephrine also showed marked edema, but no diffuse hemorrhage, only localized petechiae. Animals treated with desoxycorticosterone and epinephrine showed pulmonary edema, which was almost without hemorrhage. However, this latter group in general showed varying degrees of clear serous ascites, with edematous engorgement of some tissues. Detailed pathological studies will be reported later in a separate communication.

Discussion. The induction of sclerotic lesions in arteries, produced by excessive dosage of epinephrine, has been attributed to two possible mechanisms. One of these is the effect of anoxemia on the vessel walls as a result of the severe vasoconstriction. As a part of this action, the blood flow in the vasa vasorum may be indirectly affected. The second mechanism is that of an effect of epinephrine on the cellular metabolism, especially the biochemical chain of oxidative catalysis. Study of the concentration of some of the oxidative enzymes in human aortas, cytochrome C, and alloxazine-adenine dinucleotide and phosphopyridine dinucleotide (coenzyme I and II), showed a marked decrease of these enzymes in sclerotic aortas which was roughly proportional to the degree of sclerosis(8). It is known that thyroxin enhances the degree of vasoconstriction caused by epinephrine, and also increases the oxygen consumption of tissue generally; in the light of this, the high and severe incidence of sclerotic lesions in rabbits treated with both thyroxin and epinephrine becomes more understandable. The stress on the cardiovascular system, as a result of this combined treatment, further increases the oxygen need of the tissues involved. This cardiovascular stress was evidenced in the permanent tachycardia seen after several days of epinephrine and thyroxin treatment. In many cases, the normal heart rate of approximately 200 per minute was increased to as high as

360 per minute.

The almost complete absence of sclerotic changes in the group of animals treated with epinephrine and desoxycorticosterone is difficult to explain. Further, the Selye group(9), working on chicks and rats, obtained hypertension and vascular changes with the use of desoxycorticosterone. The well known action of desoxycorticosterone in the regulation of cell membrane permeability and its effect on electrolyte balance may be involved in facilitating detoxication in a state of hypoxic metabolism. When thyroxin is added to this treatment desoxycorticosterone failed completely to inhibit the sclerotic changes. It is possible that the permeability changes due to desoxycorticosterone are no longer sufficient to compensate for the enormous catabolic injury to the tissues of the vessels.

Summary. Thyroxin and epinephrine treatment in rabbits was shown to produce aortic sclerosis in a greater percentage of cases, and a more severe grade of such sclerosis, than epinephrine alone. Desoxycorticosterone decreases the amount of sclerosis due to epinephrine alone but failed to influence the sclerosis due to the combined epinephrine-thyroxin treatment.

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Effect of Cortisone Administration upon Nucleic Acid Composition of Rabbit Liver.* (19231)

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Though purines appear in increased amounts in urine of both animals and humans treated with cortisone or ACTH(1-4), it is not clear whether the uricaciduria is merely a reflection of decreased tubular reabsorption of uric acid(1,4), or results partly from lymphoid tissue destruction, since this atrophies following the administration of ACTH(5-7). A portion of the pentose nucleic acid (PNA) of hepatic cells of animals is labile and can be reduced by chemical injury(8,9) and starvation(9-11), and returns readily during recovery from either type of stress. Because of these observations, experiments were planned to demonstrate whether cortisone could reduce the amount of PNA in the liver.

Plan of experiments. Cortisone was injected intramuscularly in daily doses of 25 mg for 1, 2, 3, and 6 days in 10 albino rabbits, 1-2 kg in weight. The animals were sacrificed 24 hours after the last dose of cortisone. In addition, 2 animals received cortisone for 3 days and were sacrificed 9 days later. Six animals served as controls. The animals were stunned by a blow on the head, then exsanguinated by severing the hepatic vein. The livers were dissected free and weighed after removal of the gallbladder. A 2-4 g portion of the liver was weighed wet, then dried first over a water bath, then in an oven at 100°C to constant weight. A second portion (2-4 g)

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