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The Effect of Arterenol and Epinephrine on Experimental Arteriopathy

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THE EFFECT OF ARTERENOL AND
EPINEPHRINE ON EXPERIMENTAL ARTERIOPATHY

by

Bernard Friedman

A thesis submitted to the Faculty of the Graduate
School of Loyola University in
partial fulfillment of the requirements
for the Degree of Master of Science

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LIFE

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Publications:

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2. Experimental Arteriopathy Spontaneous, Epinephrine-Thyroxine and Cholesterol-Induced Forms. American Journal of Pathology, 1955, LXVI, No. 4, pp 717-724.
3. Influence of Adenosine Triphosphate, Adenosine Monophosphate and Heparin in Experimental Arteriopathy. Circulation Research, Vol. III, No. 4, July, 1955 pp. 374-377.

(continued)

4. Effect of Arterenol and Epinephrine on Experimental Arteriopathy. *Journal of Phar. and Expt. Therapeutics* Vol. 113, No. 1, Jan., 1955.
5. Progesterone and Alpha Tocoopherol in Experimental Epinephrine-Thyroxine Arteriosclerosis and in Cholesterol Induced Atherosclerosis. *Circulation* Vol. XII, No. 3, Sept., 1955.
6. Spontaneous Arteriosclerosis in Epinephrine-Thyroxin and in Cholesterol Induced Arteriopathy. *Circulation*, Vol. X, Oct., 1954.

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CHAPTER I

INTRODUCTION

The various arteriopathies have been defined and classified as follows: (Report, Nomenclature Committee, American Society of Arteriosclerosis, 1953)

A. Degenerative Arteriopathies

1. Atherosclerosis

A disease characterized by plaque-like deposits in the intima which contain cholesterol, neutral fat lipophages. The lesions tend to enlarge, become fibrotic and sometimes calcified, may encroach upon the lumen of the artery and develop degeneration on the intimal surface which may lead to thrombotic occlusion. Factors which may be concerned in the pathogenesis are heredity, disturbances in lipid and

carbohydrate metabolism, high caloric and fat intake, and various endocrine disturbances.

2. Medial Arteriosclerosis (Moenckeberg's)

A disease characterized by wide spread deposition of calcium and fibrous tissue in the media, usually in small areas and sometimes in circumferential rings. It occurs rarely in infants, children and young adults and is most commonly a disease of later life which tends to progress with aging. The etiology is unknown and may be multiple. Reduction of the arterial lumen may occur but is rare. (in peripheral arteries)

3. Arterionecrosis

a. Cystic medionecrosis. A disease characterized by cystic degeneration of the medial coat of the Aorta leading frequently to dissecting aneurism and sometimes aortic insufficiency. The etiology is unknown and the condition may occur in young or middle aged adults and sometimes in the terminal months of pregnancy.

b. Toxic Arterionecrosis. A disease characterized by degenerative and necrotic lesions in various parts or all of the coats of the arteries attributable to toxic substances of exogenous origin, substances elaborated by diseased or

injured kidneys or excess of substances of suprarenal origin.

- c. Arterionecrosis of physical origin. Arterionecrosis produced by gross mechanical or thermal trauma.

B. Productive or Hyperplastic Arteriopathies.

A disease primarily involving the small arteries and arterioles characterized by hyperplasia of the medial coat and to a lesser extent of the intimal coat. It is associated with or resulting from increased arterial pressure. (The Pulmonary arteries may be involved in some types of congenital heart disease.)

C. Inflammatory arteriopathies.

1. Infectious

- a. Syphilitic. A lesion produced by spirochete pallida involving primarily the thoracic aorta. Rarely other arteries, tending to produce aneurysms and aortic valve insufficiency. The disease involves primarily the vasa vasorum with perivascular cellular collections and secondary atrophy and necrosis of the muscle fibers of the medial coat.
- b. Bacterial. A disease characterized by local inflammatory and destructive changes in arteries of various parts of the body, produced by local invasion or metastatic dissemination of various bacteria particularly streptococci, staphylococci.

pneumococci and others. Mycotic aneurysms develop frequently at the site of involvement.

- c. Plasmodial. This type of arteritis usually involves small arteries associated with severe or terminal malarial infections.
- d. Viral. Arteritis usually the small arteries in various parts of the body produced by rickettsial and other virus infections.

2. Hypersensitivity.

- a. Perarteritis Nodosa (essential polyarteritis). It is characterized by widespread involvement of small arteries with segmental-necrosis of the medial coat with excessive localized periarterial cellular collections and healing by fibrosis or obliteration. It is uncertain whether all cases represent a true hypersensitivity reaction although it is quite probably that this is the etiology in some such cases. The hypersensitivity may be to drugs, antibiotics, foreign protein or other unknown agents.
- b. Arteritis associated with systemic lupus erythematosus. It is part of a more widespread collagen disease characterized by necrosis of the collagen substances leading to separation of muscle fibers, low grade inflammatory changes

and sometimes intimal proliferation and thrombosis of small arteries.

- c. Arteritis associated with scleroderma and atherosclerosis. A disease of small and medium sized arteries, usually of the extremities, characterized by fibrosis of the adventitia, slow endothelial proliferation and arterial occlusion which may lead to tissue ischemia and sometimes gangrene.
- d. Arteritis associated with rheumatic fever particularly involving the coronary arteries.
- e. Thrombotic thrombocytopenic purpura. A relatively uncommon disease of arterioles and capillaries characterized pathologically by collagen changes in the endothelium leading to localized endothelial proliferation, extensive platelet deposition and occlusion of the involved vessels with secondary thrombocytopenia and purpuric changes.

3. Chemical

Arteritis associated with or resulting from chemical injury of arteries either due to local contact from injection of chemical solutions or absorption of toxic chemicals of various types.

4. Physical

Inflammatory changes in the arteries resulting from exposure to various physical agents: light, heat, cold x-ray, radioactive substances.

5. Mechanical Trauma

Arteritis secondary to mechanical injury.

6. Undertermined or uncertain origin.

a. Thromboanglitis obliterans. A recurrent segmental, obliterative panarteritis involving the arteries and veins of the extremities and rarely the viscera, occurring almost exclusively in young adults males and tending to lead to ischemic of tissues and sometimes gangrene. The complete etiology is unknown but currently the use of tobacco in sensitive individuals is considered the most important etiologic factor.

b. Cranial Arteritis. A localized panarteritis involving chiefly the arteries of the head and scalp and occasionally those of other part of the body. It is seen almost exclusively in elderly individuals, tends to produce sudden loss of vision, more rarely loss of hearing. The lesions have the histologic appearance of granulomas, contain giant cells, produce considerable periarterial inflammation and

sometimes occlusion by endothelial proliferation and finally thrombosis. The etiology is unknown and no relation to infectious organisms has been established.

- c. Obscure primary pulmonary endoarteritis.
- d. Combined Forms of Arteriopathies

Combination of any of the aforementioned arteriopathies. The combination of atherosclerosis and medial arteriosclerosis or arterionecrosis is frequent and suggests that medial lesions may often determine the localization of atheroma in susceptible individuals.

There is a significant divergence of opinion concerning the etiology and histochemical changes which occur during the various forms of arteriopathy.

A summary of selected pertinent experimental, clinical and pathological findings will be presented as the first section of this report.

The combination of atherosclerosis and medial arteriosclerosis is frequent and suggests that medial lesions may often determine the localization of atheroma in susceptible individuals. (American Society for the Study of Arteriosclerosis, (1953).

Bell (1952) states that serious clinical disability is due to intimal atherosclerosis, not to medial calcification; but the former is so frequently superimposed upon the latter that a

distinction is difficult.

B. Theories of Etiology

1. Senescence

A highly regarded theory is one which maintains that the degenerative, debilitating, cardiovascular changes are simply reflections of the aging process. (Aschoff, 1924, Josue, 1904, Hueper, 1944, and Coutschkow, 1933). A number of facts are given to support this premise;

- a. With age, the vessels themselves undergo thickening and widening (Wilens - 1947 and Hueper - 1945).
- b. Concurrently, there is a marked degeneration of the elastic elements. (Bell - 1933, Cowdry 1933, Hueper - 1944, and Wilens - 1947).
- c. With age there is fibrotic thickening of the intima with a loosening of the binding substance of the elastic membranes of the tunica media. (Aschoff 1948, Cowdry 1944, Hueper 1944, and Wilens 1945).

The following arguments have been raised against the senescence theory:

1. The diffuse changes in gross morphology, and even the severe microscopic pathology visible in the aged arteriosclerotic individual are not sub-

stantially dissimilar from the focal lesions which prevail initially.

2. Arteriosclerosis is not a unique circumstance of the aged. On the contrary, there is excellent evidence that its occurrence is common, even in the very young. (Bordley 1926, Cowdry 1933, Gould 1951, Handlesman 1906, and Hueper 1944).
3. The age theory also fails to explain the wide variations in the incidence of this disease namely, its less frequent occurrences in the Negro and in women.

2. Toxin Theory.

The presence in the body of endogenously or exogenously originating autotoxic substances damaging to the vascular wall, has been advanced as the cause of arteriosclerosis. (Faber 1949, Hueper 1944, Saltykow 1908, and Winternitz 1937).

3. Mechanical Trauma.

Aschoff, 1924, Leary, 1938 Solowew, 1929 and others have experimentally induced lesions in the vascular tree by such diverse procedures as adventitial dissection, application of silver nitrate, turpentine, zinc chloride, or heat to the vascular wall and even pulverization or crushing of the artery. Such trauma usually resulted in median necrosis and intimal thickening, which is only in a limited sense, histologically comparable to the human form of arteriosclerosis. Gould, 1951 and Moschowitz, 1951 have

made reference to mechanical or psychic trauma as playing an additive roll in the sclerogenic process. The precise nature of this postulated trauma was not explained.

4. Hypoxia (and its influence on medial arteriosclerosis).

A vast fund of literature has accumulated describing a number of specific sclerogenic agents which have produced their particular lesions, presumably by persistent interference with the oxidative metabolism and nutrition of the vascular wall. While sclerosis is the end product, the route by which these various agents produce their respective destructive pathology is not clear. The hypoxia (or anoxemia) theory of arteriosclerosis has been related to numerous etiologic factors. Both hypotonic and hypertonic agents have been suggested as factors in the production of such hypoxia. These precursors or precursing conditions have been classified by Hueper - 1944. According to Hueper 1944, hypotonic conditions of endogenous origin lead to a stagnant anoxia, followed by increased permeability of the relaxed vascular wall. Hypertonic conditions of endogenous origin may be followed by decreased permeability and constrictive ischemia (anoxia). Hueper concludes that the evidence available indicates that local or general vascular hypertonic of sufficient intensity and duration causes the development of fibrous intimal thickenings and medial degenerations of fibrosing, hyaline and calcinotic types.

5. Hormonal Factors

a. Epinephrine

There are numerous experiments relating epinephrine and other hormones to the production of arteriosclerosis. Repeated injections of epinephrine were first used to produce sclerosis of the aorta by Josue in 1903. His experimental results have been confirmed and elaborated by Revault and Bouysset 1928, Lortat 1904, Waters and de-Sute Nagy 1950, Kulbs 1921, Kleinberger 1907, Pearce 1906, Loeb 1907, Aschoff 1908, Handelsman 1906, Kaiserling 1907, Cowins 1906, Lange 1924, Reab 1939, and Paul 1931, Oester and Davis 1952 and many others. Theoretical considerations involved in the production of such aortic sclerosis included generalized interference with the oxidative metabolism of the aorta, or more specifically, a lowering of the oxidation enzyme concentration in the aorta. (Hueper 1944) Baska 1946 ably surrounding this theoretical contention by demonstrating that the cytochrome c, adeninealloxazine dinucleotide, and coenzyme I and II, were definitely lower in the epinephrine induced aortic sclerosis. There is not enough evidence to assuredly identify this particular type of lesion with the form common to humans.

The direct pharmacologic effects of epinephrine on cytochrome levels, however, are not clearly known.

Adrenalectomy in rats prevent the cardiovascular hyalinosis and sclerosis otherwise produced by anterior pituitary preparations. .This is so, even in animals kept in good condition by the administration of maintenance doses of adrenocortical extracts. (Selye 1950)

Case reports of human children (14 years) with pheochromocytoma and concomitant atherosclerosis further bear on the relationship of epinephrine to arteriopathy. In one 14 year old child, the atherogenic process was uncommonly extensive and severe, and was attributed to circulating epinephrine. (Kremer D. W. 1936)

B. Thyroxine

Mardones, Monsalve, and Plaza de las Reyer 1951 working with tissue enzyme cytochrome C, have demonstrated the following:

- a. Thyroid hormone concentration and cytochrome C concentrations are positively correlated.
- b. Low levels of cytochrome C yield a quicker and more severe cholesterol induced atherosclerosis.

There has been much speculation concerning the roll of thyroid, as well as other hormones, in the process of sclerosis of arteries. The status of thyroid products in producing or inhibiting arteriosclerosis is apparently paradoxical.

In 1940, Lortst and Sabareanu by surgical extirpation of the thyroid gland, inhibited the aortic sclerosis which they otherwise produced with repeated injections of epinephrine. More recently, thyroid hormone has been employed as an agent to inhibit the formation of cholesterol induced atherosclerosis.

Stangler and co-workers, et al administered thyroid preparations to animals on a cholesterol diet such that ordinarily atherosclerosis would be produced. The results were an almost invariable inhibition of the hypercholesterolemia and retardation or complete stoppage of the expected development of atherosclerotic plaques.

Stangler, et al, 1949, showed such inhibitions by thyroid were not produced in the chick.

Oester and Mikulicich 1951, have exaggerated the sclerotic lesions induced by epinephrine, with the concomitant injection of thyroid. When thyroid alone was injected, these authors could not produce sclerotic lesions in the animals tested. Friedman 1955 injected 0.15 mg/kg of thyroxine subcutaneously for a period of two weeks to a group of 15 rabbits. Only one rabbit showed any aortic changes. This result is perplexing because thyroid increases the level of the cytochrome C (Mardones, et al 1951).

C. Adrenal Cortex

Leriche and Freulich, 1939 caused arteriosclerosis in animals by implantation of adrenal cortex.

Selye and Stone 1949 produced aortic sclerosis with

desoxycorticosterone acetate (DCA).

D. Miscellaneous Etiology

Arterial vessel exhibiting sclerotic lesions have been associated with long standing diabetes. Gibbs, Buckner et al (1933) reported that the serum cholesterol concentration of diabetics with advanced arteriosclerosis is raised.

Rabinowitsch (1938) attributed the arteriosclerosis of diabetes to the hyperlipemia accompanying the latter disease.

Examination of aortas and pulmonary vessels by Root (1936) indicated that neither hypertensives nor diabetics exhibited a greater incidence or degree of arteriosclerosis.

Perhaps the best resume of the relationship between diabetes mellitus and arteriosclerosis is the work of Moschowitz (1951), who reaches the following conclusion:

1. Diabetes mellitus does not cause hyperplastic arteriosclerosis. Hyperplastic arteriosclerosis as rhetorically defined by Moschowitz is an entity separate in morbid anatomy as well as pathogenesis from arteriosclerosis.
2. Diabetics exhibit no greater degree of arteriosclerosis.
3. Increased hyalinization, due to diabetes itself, or perhaps to hypertension, does yield greater arterial lesions in the pancreas and in the Islets of Langerhans (capillary sclerosis).

Wilens (1947) noted that the incidence of arteriosclerosis was lower in chronic alcoholics. This was taken to mean that damage to the liver was a protection against the atherosclerotic process. However, Rabinowitsch (1948) witnessed a premature onset of arteriosclerosis in diabetics with liver damage. Gofman and Pierce (1951) conclude that during pathological conditions, the liver may be a depot for the formation of Sf 10-20 molecules but they disagree with the suggestion that hepatitis protects against atherosclerosis. In this respect the predponderance of evidence is against a protective effect by liver damage.

Wilens 1951, reinvestigated and then restated an older theory of Anitschkow (1933). This states that there is a constant passage of fluid through the walls of the arteries in the direction from the lumen to the adventitia, and that arteriosclerosis results when there is a disturbance in this transport.

The exact relationship of xanthomatosis and nephrosis to arteriosclerosis is not known; but the lipid-protein distribution is strikingly similar to that of atherosclerosis. (Russ, Barr, Eder, 1951).

E. Spontaneous sclerosis

Listed below is a survey of the literature pertaining to the occurrence of spontaneous arterial disease in rabbits.

Medinger and Loeb, 1906 "Spontaneous arterial disease has not been observed in rabbits so far as is shown by all the literature. We, ourselves, have never found such lesions in about 100 rabbits

that were investigated with that in view". Lesions were most frequently seen that have been described by others in the abdominal aorta, and less frequently in the iliac arteries. There was a greater tendency for the lesions (to appear about the mouths of the branching vessels, (As in the thoracic region). "It is by no means uncommon to see lesions in the middle or deeper portions of the media or, less frequently, involving the outer portion of the media and adventitia. The lesions of "normal" rabbits consisted of:

- a) calcified area
- b) cellular infiltration
- c) Hyaline and granular degeneration of muscle and elastic tissue.

Miles A. 1907 reported that 17 or (34.7%) of 49 rabbits showed spontaneous arterial lesions as compared to 17 or (27.8%) of 61 rabbits that received adrenalin.

Hill, Miner 1910 The occurrence of spontaneous arterial disease in the rabbit is an important factor in the experimental study of vascular disease, and a factor the status of which must be definitely determined before the result of experimentation along this line can be definitely accepted. Spontaneous lesions were found in 15% of 210 presumably normal animals. Histologically the common type of spontaneous sclerosis cannot be distinguished from that due to adrenalin. Macroscopically, the lesions are limited to a few foci at the origin of the aorta. These

spontaneous lesions apparently explain the results previously ascribed to single injections of adrenalin for a number of repetitions of the "single injection" experiments have given negative results.

Davis, Oester and Friedman 1954 report that spontaneous lesions were found in only 1 of 71 animals or 1.4%.

Miller, J. L. 1907, summarizes several large series of observations on normal animals without the discovery of spontaneous lesions.

Pearce, R. M. 1908 in his study found lesions in 6% of the animals examined.

Levin, 1909-10 On gross examination, 31 of 240 rabbits 13.0% showed gross spontaneous lesions of the arteries. Of the remaining 209, 78 or 37.3% presented minute lesions visible under the microscope. The lesions showed either the degeneration of the media including the muscular fibrous tissue coat with the elastic fibers preserved, or the same degeneration of the media with loss of muscular and elastic fibers and deposition of calcium. In other vessels, the main condition was proliferation of the endothelial cells of the intima.

Solmann - 1948 reported (3-30% Spontaneous sclerosis in rabbits). "There is a spontaneous atheroma in rabbits of 3-30% that is identical to the atheroma produced by epinephrine."

Oester and Davis 1955 reported that no sclerosis was found in twelve rabbits that were injected intravenously with a

solution of sodium chloride, benzyl alcohol, sodium carboxymethylcellulose and tween 80.

The above findings seem to indicate that gross spontaneous arterial disease is not a significant factor in this study.

CHAPTER II

The Statement of the Problem

Josue in 1903 used repeated injections of epinephrine to produce a sclerosis of the rabbit aorta. Many other investigators (Lange, 1924, and Heuper, 1944) have confirmed these experimental results. Mikulicich and Oester (1951) observed that combined injections of epinephrine and thyroxine resulted in an apparently greater production of experimental sclerosis in the aorta of the rabbit. Davis and Oester (1952) extended these results. Using epinephrine and thyroxine, they obtained a 90 per cent incidence of sclerosis, as compared to a 30-50 percent incidence when epinephrine alone is used.

In 1946, von Euler demonstrated the presence of levo-arterenol (also known as l-arterenol, nor-epinephrine, nor-adrenalin) in mammalian tissue. Levo-arterenol was first detected

in extracts of organs, such as the spleen, the heart, and the liver, and it was subsequently shown that it was a constantly occurring and specific constituent of adrenergic nerves (von Euler 1946, 1948). Such evidence provided the basic support for the theory that levo-arterenol is one of the adrenergic neurotransmitters (von Euler, 1951). Tainter, Tullar, and Luduena, in 1948, succeeded in the separation of the isomers of the synthetically prepared arterenols. This resolution opened an intensive and wide-spread investigation into the physiologic and pharmacologic importance of arterenol.

Since 1903, epinephrine has been used by many investigators, to produce arteriopathy. As far as can be determined, all of this work has been carried out using an epinephrine which contained some percentage of arterenol as an unknown constituent. In 1949, Auerbach and Angell showed that routine U.S.P. epinephrine, extracted from the adrenal medulla of cattle, contained between 10 to 16 per cent arterenol. Goldenberg (1948) and Goldenberg and others (1949) have reported results which are in agreement with this finding.

With these facts in mind, the purpose of our work was to produce arteriosclerotic lesions of the aorta and to compare the effects of 100 percent epinephrine and 100 percent arterenol, with and without thyroxine, in the production of arteriopathy in the rabbit. It is of obvious interest to isolate the effects of these two closely related compounds, if possible.

CHAPTER III

Method and Material

A total of 125 young adult rabbits, of both sexes, weighing 2.5 to 3.5 kilograms, were used. Arteriopathy was produced as follows: each rabbit was given 25 mcg/kg. of epinephrine or arterenol. This was injected very slowly by ear vein for two consecutive days. On the third day, the dose was increased to 40 mcg/kg. On the fourth day, it was increased to 50 mcg/kg. The regimen was maintained for eleven more days, making a total of fifteen days of treatment. Thyroxine was administered subcutaneously in the region of the middle of the back, daily for fifteen days, at a constant dose of 0.15 mcg/kg. of body weight. All the animals surviving on the sixteenth day were sacrificed by intravenous lethal dosage of pentothal. The heart and the aorta down to the iliac bifurcation were removed.

Gross examination was made for aortic pathology. The observations with which we were mainly concerned were the frequency and severity of gross lesions in the aorta. An accurate comparison of sclerotic plaques in different animals is not easily accomplished. For purposes of differentiation, however, we undertook their gradation on the following basis: 0, no plaques; 1 mild single patches (plaques); 2, mild, scattered patches; 3, severe, extensive patches; 4, widespread, confluent and extensive patches. The aortas were preserved in 10 per cent formaldehyde, and microscopic sections were prepared of selected specimens. Routine hematoxylin-eosin staining was used.

Other groups of rabbits were treated in a manner similar to that described above, except the arteriopathy was induced by different regimens listed below. The dosages of the several substances were the same in all groups. An additional group of 13 rabbits, which had not received any drug or treatment, was examined for possible spontaneous sclerosis.

CHAPTER IV

Results

The results of Table VII show that with each group tested, a sclerosis of some of the rabbits treated was found in each case. When commercial epinephrine (with its 10-15% of arterenol) was injected there was an average degree of sclerosis of 0.9. When thyroxine was added to the commercial epinephrine, the average degree of sclerosis was increased to 2.3. This group also showed the greatest number of third and fourth degree sclerosis. In contrast, the 100 per cent epinephrine had an average degree of sclerosis of 0.6 with no three or four degree scleroses.

The arterenol group of animals showed an average degree of sclerosis of 0.5 but had two third degree and one fourth degree sclerosis. When Thyroxine was added to the arterenol there is found, as with epinephrine, an increase in the average degree

of sclerosis to 2.0. There were also seven third degree scleroses and two fourth degree scleroses.

The Control group of thirteen rabbits showed no gross arteriosclerotic changes with an average degree of sclerosis therefore of zero.

Table VIII is a statistical evaluation of the data with reference to the per cent incidence of macroscopic sclerosis. The probabilities listed were obtained by using the Chi Square Test with the Yates correction. A value of less than 0.05 is assumed significant. A value of more than 0.05 is assumed not significant. Animals whose death occurred before the 6th day of treatment were not included in this biometric analysis.

From this data we again see that in each group of animals treated, some per cent incidence of sclerosis was produced. The commercial epinephrine produced a sclerosis in ten of twenty animals for a 50% incidence of sclerosis. When thyroxine was added a sclerosis was produced in seventeen of twenty animals an 85% incidence of sclerosis. The probability for both groups was 0.01 when compared to the control group of zero per cent sclerosis. The 100% pure epinephrine alone produced a 48% incidence of sclerosis with ten of twenty one rabbits exhibiting gross sclerotic changes. The probability for this group was less than 0.05 and was assumed significant.

Arterenol animals had a 17% incidence or four of twenty three rabbits having sclerosis. This group showed a probability

of greater than 0.1 and was therefore not significant. This result is considered further in the discussion.

Upon the addition of thyroxine to the arterenol regimen a sclerosis was produced in seventeen of twenty two animals, a 77% incidence of sclerosis. The probability for this group was less than 0.01 which is significant.

The following groups of animals were used:

Group 1. Epinephrine hydrochloride (Commercial and Thyroxine E-T.

Group 2. Epinephrine hydrochloride (Commercial -E1

Group 3. 100 per cent Epinephrine Bitartrate - E2

Group 4. 100 per cent Arterenol Bitartrate - A
Mintrop-Stearn-Levophed

Group 5. 100 per cent Arterenol Bitartrate and
Thyroxine - A-F

Group 6. No treatment - C

The commercial epinephrine which was used was found to contain 10-15 per cent of arterenol by means of a spectrophotometric determination. This agrees with the findings of others, as to the amount of arterenol present in routine commercial U. S. P. epinephrine. Tables I to VII provide a summary of the protocols of these experiments. Table VIII is a summary of the data from these experiments.

CHAPTER V

DISCUSSION AND CONCLUSION

In this work, major emphasis was placed on the incidence of grossly evident sclerosis not, however, to the exclusion of microscopic studies. This criterion was used for the practical reason that clinical arterial disease of any type invokes its greatest damage when the pathological deposits or changes encroach on the lumen of the vessel and thereby interfere with delivery of blood.

While experimental arteriosclerosis of the media is not commonly associated with pathological encroachment on the arterial lumen, it is perhaps noteworthy to reconfirm that the tunica media is of great importance in the physical composition of the artery. This greater importance of the media is not alone restricted to its greater size, but with its muscle content (except small

calibre vessels) there is every reason to believe it is a more active center of metabolic activity than is the intima or adventitia.

Clinical pathological studies (Crawford and Levene) 1953, show in more than 100 cases, a thinning of the media in otherwise uncomplicated atherosclerosis. In view of these and other findings and observations (American Society of Arteriosclerosis, Nomenclature Committee, 1952) it no longer seems wise to consider clinical or experimental arteriopathy in terms of the intima exclusively, but rather of the artery as a total entity.

It has been demonstrated often that arterenol has an action on many tissues similar to epinephrine. This may also apply to sclerogenic properties. With reference to the severity factors in Table VIII it can be seen that the severity factor for epinephrine (commercial) of 42.5 is higher than the severity factor of pure epinephrine 28.8 and both of these epinephrine factors are higher than the severity factor of arterenol alone, 8.5. Again it can be observed that the severity factor for epinephrine and thyroxine is 195.5 as compared to a severity factor of 154 for arterenol and thyroxine.

The earlier work previously mentioned has established the effect of commercially marketed epinephrine in relation to the production of arteriopathy in rabbits. Such arteriopathy is apparently augmented when thyroxine is added to the sclerogenic schedule (Mikulicich and Oester, 1951). Commercial epinephrine

has been shown, by the reports of several workers, to contain from 10 to 18 per cent arterenol. Before the present work it was entirely possible that this contaminating arterenol may have been responsible for the sclerosis.

The results, as reported here indicate that both epinephrine and arterenol can produce a sclerosis of the sorts of the rabbit. Arterenol (100%) produced a lesser incidence of sclerosis than either 100 per cent epinephrine or commercial epinephrine. The 100 per cent arterenol produced a 17 per cent incidence of sclerosis, while 100 per cent epinephrine produced a 48% incidence of a similar sclerosis. The 17 per cent incidence of sclerosis with arterenol is not statistically significant. However, this arterenol sclerosis assumes a probability of less than 0.01 when the results from previous controls of one sclerosis in 71 animals are added to this study. The 48 per cent incidence of sclerosis with epinephrine (100 per cent) was comparable to the 50.0 per cent incidence of sclerosis which was obtained when commercial epinephrine (epinephrine plus 10-18 per cent arterenol) was used. When thyroxine was added to each of the above agents, there was an increase in the incidence and severity of the arteriopathy. Upon the addition of thyroxine, the per cent incidence of sclerosis with arterenol was increased from 17 per cent to 77 per cent, while the per cent incidence of sclerosis with commercial epinephrine was increased from 50 to 85 per cent. This 85 per cent incidence is comparable to the 90 per cent

incidence reported by Davis and Ooster, 1952.

The lesions of the aorta produced by epinephrine-thyroxine and arterenol are histologically, essentially similar. They represent, primarily, a medial sclerosis and necrosis. A comparison of these lesions is shown in Figure 3 and Figure 4 of rabbit aortas with medial and intimal damage.

There was no gross spontaneous arteriopathy in the group of animals which received no treatment of any kind. This leads to the conclusion that spontaneous aortic lesions are not a significant factor in this experiment. This is further confirmed by previous saline control studies from the same rabbit population.

Even if we choose to ignore or minimize the non-routine findings we have seen in the intima, the investigations into the production of medial sclerosis have much fundamental significance. This is especially true when we consider the correlations which are said to exist in man between medial sclerosis and intimal atherosclerosis, as reported by Bell (1952), Crawford and Levene (1953), and the American Society for the Study of Arteriosclerosis (1953).

It has been demonstrated that both epinephrine and arterenol may be used to induce a form of experimental medial arteriosclerosis in the aorta of the rabbit. There is some evidence that intimal proliferation may also be induced by this

technique (Figure 3 and Figure 4), although this is not an invariable finding. The general appearance of medial sclerosis and the less frequent intimal proliferation were essentially the same (except for incidence), whether thyroxine was used or not.

From the results reported here, it is not shown what the exact role of epinephrine and/or thyroxine is.

CHAPTER VI

SUMMARY

1. The effect of epinephrine (100 per cent) in producing aortic arteriopathy in rabbits is similar to that of commercial U. S. P. epinephrine (epinephrine plus 10-18 per cent arterenol).
2. Arterenol (100 per cent) produces a type of arteriopathy similar to that of epinephrine. This involvement is of a markedly lesser incidence than that produced by either 100 per cent epinephrine or commercial epinephrine.
3. Thyroxine, added to the 100 per cent arterenol regimen, increased the incidence of arteriopathy, significantly.
4. Commercial epinephrine and thyroxine produced an incidence of arteriopathy which corresponds closely with the reports of previous investigators.

5. The arteriopathy produced by epinephrine or arterenol alone, or in combination with thyroxine, is essentially a medial sclerosis and necrosis. There is, in some instances, also a concomitant intimal proliferation.

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TABLE I

Epinephrine and Thyroxine

January, 1952

<u>Animal</u>	<u>Beginning</u> <u>Wt./K.G.</u>	<u>Final</u> <u>Wt./K.G.</u>	<u>Total Number</u> <u>of injections</u>	<u>Degree of</u> <u>Sclerosis</u>
101	2.3	2.2	11	4
102	2.1	1.9	15	4
103	2.2	2.1	9	0
104	2.2	2.0	15	3
105	1.9	1.8	15	2
106	2.1	2.0	3 disregard	0 disregard

Total animals used - 6

March, 1952

1	2.0-	1.8	15	2
2	2.5	2.2	10	2
3	2.4	2.3	15	1
4	2.4	2.2	15	3
5	2.2	2.2	12	3
6	1.8	1.7	13	2

Total Animals - 6

September, 1952

1	2.3	2.0	15	3
2	2.0	1.8	8	4
3	2.0	1.9	15	0
4	2.1	2.0	15	3
5	2.2	2.0	10	2

Total Animals - 5

TABLE I (cont'd)

Epinephrine and Thyroxine

August, 1953

<u>Animal</u>	<u>Starting wt. wt./K.G.</u>	<u>wt./ K.G.</u>	<u>Total number of injections</u>	<u>Degree of sclerosis</u>
1	2.1	1.9	15	0
2	2.5	2.2	15	2
3	2.3	-	5 (disregard)	
4	2.1	1.8	15	3
5	2.2	1.9	7	3

Total animals - 5

Totals

<u>Number of Rabbits</u>	<u>Death before 6 days</u>	<u>Death 6 to 15 days</u>	<u>Number of Animals Sacrificed</u>
22	2	8	12

Degree of Sclerosis

	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
<u>Number of Animals</u>	3	1	6	7	3

TABLE II

Epinephrine - (commercial)

<u>Animal</u>	<u>Starting Wt./K.G.</u>	<u>Ending Wt./K.G.</u>	<u>Total Number of injections</u>	<u>Degree of Sclerosis</u>
1	1.9	2.0	8	3
2	2.1	-	3	Disregard
3	2.0	2.1	11	3
4	2.1	2.2	13	0
5	2.4	2.3	15	0
6	1.9	2.0	15	2
7	2.4	2.4	7	0

Total Animals - 7

January, 1952

1	2.1	2.2	15	1
2	2.2	-	2 Disregard	-
3	2.0	2.1	15	1
4	2.1	2.2	15	0
5	2.3	2.3	15	1

Total Animals - 5

June, 1952

1	2.2	2.3	15	0
2	2.0	1.9	9	2
3	2.1	2.2	15	1
4	1.8	2.0	11	0
5	2.3	2.3	10	0

Total Animals - 5

TABLE II

Epinephrine - (commercial) - Cont'd.

December, 1953

<u>Animal</u>	<u>Starting</u> <u>Wt./K.G.</u>	<u>Finishing</u> <u>Wt./K.G.</u>	<u>Total Number</u> <u>of injections</u>	<u>Degree of</u> <u>Sclerosis</u>
1	2.4	2.4	15	0
2	2.3	2.3	15	1
3	2.1	2.1	15	0
4	1.8	2.0	15	0
5	2.2	2.3	15	2

Total Animals - 5

Totals

<u>Number of Rabbits</u>	<u>Death Before</u> <u>6 days</u>	<u>Death 6 to</u> <u>15 days</u>	<u>Number of</u> <u>Animals</u> <u>Sacrificed</u>
22	2	7	13

Degree of Sclerosis

	0°	1°	2°	3°	4°
<u>Number</u> <u>of</u> <u>Animals</u>	10	5	3	2	0

TABLE III

Epinephrine (pure)

January, 1953

<u>Animal</u>	<u>Starting Wt./K.G.</u>	<u>Ending Wt./K.G.</u>	<u>Number of Injections</u>	<u>Degree of Sclerosis</u>
1	2.4	2.4	15	2
2	2.0	2.1	15	0
3	2.1	2.2	15	0
4	1.8	1.8	12	1
5	1.9	1.8	15	0

Total animals - 5

March, 1953

6	1.8	1.7	13	2
7	1.9	2.1	15	0
8	2.3	2.4	10	0
9	2.1	2.1	15	1
10	2.2	2.1	15	0
11	2.0	1.9	15	1

Total animals - 6

TABLE III

Epinephrine - (pure) Cont'd.

June, 1954

<u>Animal</u>	<u>Starting Wt./K.G.</u>	<u>Ending Wt./K.G.</u>	<u>Number of injections</u>	<u>Degree of Sclerosis</u>
1	2.1	2.2	15	1
2	2.2	2.1	15	1
3	1.8	1.8	15	0
4	2.0	2.1	9	0
5	2.5	2.4	15	1
6	2.8	2.9	15	0
7	2.3	2.3	15	2
8	2.0	1.9	15	0
9	2.3	2.5	15	1
10	2.5	2.4	15	0

Total Animals - 10Totals

<u>Total Animals</u>	<u>Death Before 6 days</u>	<u>Death 6 to 15 days</u>	<u>Number of Animals Sacrificed</u>
21	0	4	17

Sclerosis

	0°	1°	2°	3°	4°
Number of Animals	11	7	3	0	0

TABLE IV

Arterenal

June, 1952

<u>Animal</u>	<u>Starting Weight/K.G.</u>	<u>Ending Wt./K.G.</u>	<u>Number of Injections</u>	<u>Degree of Sclerosis</u>
5	2.1	2.2	15	0
6	2.3	2.3	12	0
7	2.0	2.1	15	0
8	1.9	2.1	15	0
9	2.2	2.3	15	0

Total Animals - 5

September, 1952

1	2.2	2.3	15	0
2	2.1	2.2	15	0
3	2.0	2.0	15	3
4	2.1	2.3	15	0
5	1.9	2.0	10	0

Total Animals - 5

March, 1953

1	2.3	2.3	15	0
2	2.1	2.2	15	0
3	2.0	2.3	15	0
4	2.0	2.1	15	0

Total Animals - 4

TABLE IV

Arterenol (cont'd.)

December, 1953

<u>Animal</u>	<u>Starting weight/K.G.</u>	<u>Ending wt./K.G.</u>	<u>Number of Injections</u>	<u>Degree of Sclerosis</u>
1	2.0	2.0	15	0
2	2.2	2.4	15	0
3	2.1	2.2	15	4
4	2.3	2.3	15	0

Total Animals - 4

1954

1	1.7	2.0	15	0
2	1.9	2.1	15	0
3	1.9	2.0	15	3
4	2.2	2.3	15	1
5	2.1	2.1	15	0

Total Animals - 5

TOTALS

<u>Number of Rabbits</u>	<u>Death Before 6 days</u>	<u>Death 6 to 15 days</u>	<u>Number of Animals Sacrificed</u>
23	0	2	21

Sclerosis

	<u>0°</u>	<u>1°</u>	<u>2°</u>	<u>3°</u>	<u>4°</u>
<u>Number of Animals</u>	19	1	0	2	1

TABLE V

Arterenal and Thyroxine

June, 1952

<u>Animal</u>	<u>Starting Wt./K.G.</u>	<u>Ending Wt./K.G.</u>	<u>Number of Injections</u>	<u>Degree of Sclerosis</u>
0	2.1	-	2 disregard	-
1	2.4	2.3	15	3
2	1.9	1.9	6	3
3	2.2	2.0	14	4
4	2.1	2.0	10	0
5	2.3	2.2	15	0

Total Animals - 5

March, 1952

1	2.5	2.5	15	2
2	2.1	2.0	15	1
3	2.4	2.2	11	3
4	2.0	1.9	15	2
5	2.3	2.3	10	3

Total Animals - 5

January, 1953

1	2.1	2.0	13	3
2	1.8	1.8	15	4
3	2.3	2.1	15	3
4	2.2	2.1	11	1

Total Animals - 4

TABLE V

Arterenol and Thyroxine - Cont'd.

October, 1953

<u>Animal</u>	<u>Starting Wt./K.G.</u>	<u>Ending Wt./K.G.</u>	<u>Number of Injections</u>	<u>Degree of Sclerosis</u>
1	2.1	2.0	9	2
2	2.3	2.2	12	0
3	1.9	2.0	15	0
4	2.0	2.0	15	2
5	2.1	-	4 disregard	-

Total animals - 5

February, 1954

1	1.8	1.7	15	2
2	2.1	2.0	15	0
3	2.4	2.2	15	2
4	2.2	2.1	15	3

Total animals - 4

TOTALS

<u>Number of Rabbits</u>	<u>Death before 6 days</u>	<u>Death 6 to 15 days</u>	<u>Number of Animals Sacrificed</u>
24	2	10	12

	<u>0°</u>	<u>1°</u>	<u>2°</u>	<u>3°</u>	<u>4°</u>
<u>Number of Animals</u>	5	2	6	7	2

TABLE VI

Control

<u>Animal</u>	<u>Weight</u>	<u>Spontaneous Sclerosis</u>
1	2.3	0
2	2.4	0
3	1.9	0
4	2.2	0
5	2.0	0
6	2.2	0
7	2.4	0
8	1.9	0
9	2.0	0
10	2.1	0
11	2.6	0
12	2.4	0
13	2.2	0

Previous Controls 1 out of 71 or 1.2% Sclerosis. (Oester, Davis 1955).

TABLE VII

Results - SummaryPRODUCTION OF ARTERIOPATHY
WITH EPINEPHRINE AND ARTERENOL

Treatment	Number of Rabbits	Deaths Before 6 days	Deaths 6 to 15 Days	Number of Animals Sacrificed on 16th Day	Degree of Sclerosis					Average Degree of Sclerosis
					0	1	2	3	4	
E 1-T	22	2	8	12	3	1	6	7	3	2.3
E 1 (Comsero- ial)	22	2	7	13	10	5	3	2	0	0.9
E 2 (100 per- cent)	21	0	4	17	11	7	3	0	0	0.6
A	23	0	2	21	19	1	0	2	1	0.5
A - T	24	2	10	12	5	2	6	7	2	2.0
C	13	-	-	-	13	0	0	0	0	0

E 1 = Commercial Epinephrine HCl

T = Thyroxine

E 2 = Epinephrine (100%) Bitartrate

A = Levo-arterenol (100%) Bitartrate

C = No Treatment

TABLE VIII

Statistical Evaluation of Data with Reference to
Per Cent Incidence of Macroscopic Sclerosis

Treatment ¹	Number Free of Sclerosis to Total Animals	Per Cent Free of Sclerosis	Number with Sclerosis to Total Animals	Per Cent Incidence	Severity Factor (Per Cent Incidence times avg. Deg. of Sclerosis)	² Probabili- ty (Compar- ed to Group C)
E ₁ - T	3/20	15%	17/20	85%	195.5%	0.01
E ₁ (Commercial)	10/20	50%	10/20	50%	42.5	0.01
E ₂ (Pure)	11/21	52%	10/21	48%	28.8	0.05
A	19/23	83%	4/23	17%	8.5	0.1
A - T	5/22	23%	17/22	77%	154	0.01
C	13/13	100%	0/13	0%	0-	-

1. E₁ = Commercial Epinephrine E₂ = Epinephrine (100%) A = Arterenol T = Thyroxine C = No Treatment

2. Obtained using Chi Square test with Yates Correction. A value of 0.05 is assumed significant. Animals whose death occurred before the 5th day of treatment were not included in biometric analysis.

KEY TO PHOTOMICROGRAPHS OF RABBIT AORTA

Figure 1. Normal Aorta (Gross)

Figure 2. Epinephrine - Thyroxine (Gross) severe sclerosis.

Figure 3. Epinephrine - Thyroxine

Severe sclerosis. Medial sclerosis and intimal proliferation and medial damage. (Hematoxylin and eosin stain) - x 200.

Figure 4. Arterenol Alone

Sclerosis induced by arterenol medial sclerosis and intimal proliferation (hematoxylin and eosin stain) - x 200.

Figure 5. Arterenol Alone

Sclerosis induced by arterenol medial sclerosis and intimal proliferation (hematoxylin and eosin stain) x 400.



Figure 1
Normal Aorta
(Gross)



Figure 2

Severe Epinephrine - Thyroxine (Gross) severe sclerosis and
architectural damage. (Hematoxylin and eosin stain) - x 200.



Figure 3

Epinephrine - Thyroxine

Severe sclerosis. Medial sclerosis and intimal proliferation and medial damage. (Hematoxylin and eosin stain) - x 200.



Figure 4

Arterenol Alone

Sclerosis induced by arterenol medial sclerosis and intimal proliferation (hematoxylin and eosin stain) - x 200.

proliferation (hematoxylin and eosin stain) x 400.



Figure 5

Arterenol Alone

Sclerosis induced by arterenol medial sclerosis and intimal proliferation (hematoxylin and eosin stain) x 400.

APPROVAL SHEET

The thesis submitted by Bernard Friedman has been read and approved by three members of the faculty of the Stritch School of Medicine, Loyola University.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form, and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

29 May 57

Date

J. T. Oster

Signature of Advisor