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EXPERIMENTAL ARGYROSIS

V. Hypertrophy of the Left Ventricle of the Heart in Rats Ingesting Silver Salts

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THE DEPOSITION of silver in many organs of rats ingesting silver salts for long periods has been previously reported.[1] Special reference was made to the pigmentation of the basement membranes of the glomeruli and renal tubules and of the tissue between the endothelium and the epithelium of such diverse organs as the thyroid gland and the choroid plexuses of the brain and the eye. The purpose of this communication is to present evidence that long-continued feeding of silver is accompanied by hypertrophy of the left ventricle of the heart of the experimental animal.

MATERIAL AND METHODS

Animals Used.—The ancestors of a large majority of the rats used came from Rockland Farms, New City, N. Y., of a strain almost certainly derived by H. C. Sherman, of Columbia University, from that of Osborn Mendel. Seventeen filial generations in all have been bred by mating brothers and sisters. In this way, through eight or nine years, the stock has become increasingly purebred. Each litter was divided as much as possible into a group given silver salts and another given water.

As previously described, over long periods the animals were given silver nitrate or silver chloride kept in suspension by sodium thiosulfate. In the great majority of cases these silver salts were given in 1:1,000 strength instead of drinking water. Most of the animals, including a great majority of those with essentially normal lungs which were subjected to the final statistical analysis described in subsequent pages, were killed in good health. There were relatively large numbers of spontaneous deaths among the rats eliminated from the final study because of advanced pulmonary lesions. The ages at which the animals were killed varied with many factors, including shortage of food during World War II. As much as possible, silver-treated and water-treated littermates were killed together. A few rats survived to 30 months of age.

Determinations of Blood Pressure.—Many attempts have been made in this department to determine the blood pressure of rats from the tails by the use of the method of Williams, Harrison and Grollman[2] without anesthesia. The results

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1. Olcott, C. T.: (*a*) Am. J. Path. **23**:783, 1947; (*b*) **24**:813, 1948.

2. Williams, J. R., Jr.; Harrison, T. R., and Grollman, A.: J. Clin. Investigation **18**:373, 1939.

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were not consistent, perhaps in part because of the lack of proper control of the degree of heat to which the animals were exposed. If the heat was inadequate to relax the blood vessels of the tail, an accurate reading was impossible; if it was excessive, the animal was restless, and a false reading resulted.

The aortas of about 25 rats were cannulated under either pentobarbital sodium or ether anesthesia. With both agents the blood pressure readings obtained seemed to be more closely correlated with the depth of anesthesia than with any underlying pathologic or physiologic change.

In 2 rats whose blood pressures were determined in another department of this medical school by Sobin's [3] modification of the method of Williams, Harrison and Grollman but with the use of pentobarbital sodium, the pressures fell from 121 to 92 and from 102 to 75, respectively, between determinations. Both rats died shortly after the second determinations, clearly from the effect of the anesthetic agent.

In 1941 Dr. Ben Freedman, at Mount Sinai Hospital, New York, determined the blood pressure of 6 of my rats by his modification of the method of Williams, Harrison and Grollman without anesthesia. The 3 rats with the highest blood pressure readings had the highest left ventricular weights when killed four to eight months later, but of course this series is much too small to give results of any significance.

The difficulty my associates and I have experienced in obtaining satisfactory measurements of the blood pressure of rats is unfortunately the all too common experience of others. Some authors have described differences of blood pressure in rats of different strains. With different methods of determination, the observed levels of blood pressure of normal rats fall into entirely different ranges. Thus, Woodbury and Hamilton [4] found the blood pressure of anesthetized animals to be 70 to 100 with a mercury manometer and 145 systolic and 105 diastolic with an optical one. They found the level to be 187 systolic and 138 diastolic when an optical manometer was used on the unanesthetized rat. Shuler, Kupperman and Hamilton [5] found that blood pressure was much lower when measured in the tail than when found with an optical manometer. Considering determinations of blood pressure on the tail alone, one notes very discordant normal values in the literature. They vary with the amount of heat used,[6] with the width of the cuff,[3] with anesthesia [7] and with a number of other factors.

Relation of Vascular Hypertension to Weight of Heart in Man and Experimental Animals.—Scriba [8] said that "Hypertrophy of the wall of the left ventricle and increase of the relative weight of the heart may, if the valvular apparatus is

3. Sobin, S. S.: Am. J. Physiol **146**:179, 1946.

4. Woodbury, R. A., and Hamilton, W. F.: Am. J. Physiol. **119**:663, 1937.

5. Shuler, R. H.; Kupperman, H. S., and Hamilton, W. F.: Am. J. Physiol. **141**:625, 1944.

6. Proskauer, G. G.; Neumann, C., and Graef, I.: Am. J. Physiol. **143**:290, 1945.

7. Sulkin, N. M., and Brizzee, K. R.: Proc. Soc. Exper. Biol. & Med. **64**:125, 1947.

8. Scriba, K.: Virchows Arch. f. path. Anat. **301**:321, 1938.

intact, be taken as evidence of elevation of blood pressure." Other authors[9] have come to an essentially similar conclusion.

Pässler and Heineke[10] and Mark and Geisendörfer[11] found a positive correlation between increased blood pressure and relative hypertrophy of the left ventricle in dogs with "reduced" kidney tissue. Collins[12] constricted the renal arteries of dogs and found hypertension and a relative increase in the heart's weight without any histologic changes of the kidney.

Chanutin and Ferris[13] and Chanutin and Barksdale[14] found that when vascular hypertension was induced in rats by a "reduction" of the kidney tissue, there was a correlated increase in the ratio of the weight of the heart to the surface area, the latter being a function of the weight.

Schroeder[15] found that "in rats the weight of the heart is probably a more reliable index of the presence of the hypertensive state than is one measurement, or two, of blood pressure under anesthesia."

Halpert and Grollman[16] found a positive correlation between the elevation of blood pressure and hypertrophy of the heart, especially of the left ventricle, in rats with "figure of eight" ligatures applied to their kidneys.

The weights of the hearts of many of the rats receiving water in the experiment to be described have been plotted against their body weights with results similar to those of Walter and Addis,[17] who found a straight line relationship between the log of the heart weight and the log of the body weight. Hatai's[18] values (quoted also by Donaldson[19]) are slightly higher in both categories. However, in the present series both values frequently lie much beyond the maximum values of the others quoted, clearly because so many of the rats were kept alive longer than those in the experiments of others. Cromartie[20] found that the weights of the hearts of rats with hypertension were 14 to 144 per cent heavier than those listed by Donaldson.[19]

The question arises as to the validity of using the terminal heart weight in the presence of emaciation, which was, in passing, never extreme in the present series.

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9. Evans, G.: Quart. J. Med. **14**:215, 1921. Fahr, T.: Virchows Arch. f. path. Anat. **239**:41, 1922. Murphy, F. D., and Grill, J.: Arch Int. Med. **46**:74, 1930. Rytand, D. A.: J. Clin. Investigation **17**:391, 1938. Moore, R. A.: A Textbook of Pathology: Pathologic Anatomy in Its Relation to the Causes, Pathogenesis and Clinical Manifestation of Disease, Philadelphia, W. B. Saunders Company, 1944, p. 968.

10. Pässler and Heineke: Verhandl. d. deutsch. path. Gessellsch. **9**:99, 1905.

11. Mark, R. E., and Geisendörfer, H.: Ztschr. f. d. ges. exper. Med. **74**:350, 1930.

12. Collins, D. A.: Am. J. Physiol. **116**:616, 1936.

13. Chanutin, A., and Ferris, E. B., Jr.: Arch. Int. Med. **49**:767, 1932.

14. Chanutin, A., and Barksdale, E. E.: Arch. Int. Med. **52**:739, 1933.

15. Schroeder, H. A.: J. Exper. Med. **75**:513, 1942.

16. Halpert, B., and Grollman, A.: Arch. Path. **43**:559, 1947.

17. Walter, F., and Addis, T.: J. Exper. Med. **69**:467, 1939.

18. Hatai, S.: Am. J. Anat. **15**:87, 1913.

19. Donaldson, H. H.: Rat: Data and Reference Tables for the Albino Rat (Mus Norvegicus Albinus) and the Norway Rat (Mus Norvegicus), American Anatomical Memoir 6, ed. 2, Philadelphia, Wistar Institute of Anatomy and Biology, 1925.

20. Cromartie, W. S.: Am. J. M. Sc. **206**:66, 1943.

This procedure seems abundantly justified by the experiments of Van Liere and Sleeth,[21] who found the percentage loss of the weight of the heart to parallel the loss of body weight in guinea pigs subjected to starvation.

Determination of Relative Weight of Left Ventricle.—There are practical and theoretic objections to using the weight of the entire heart which are obviated by using the weight of the left ventricle. For one thing, there is no clear line of division between the auricles and the large veins or at the origins of the aorta and the pulmonary artery. For another, there are changes in the weight of the right ventricle which are confusing and irrelevant, especially when associated with various degrees of change in the lungs. At any rate, it is felt that the most significant indication of elevated blood pressure is the weight of the left ventricle rather than that of the heart as a whole.

To obtain the weight of the left ventricle, the heart has been fixed over night in Kaiserling solution no. 1[22] (which contains sodium nitrate and sodium acetate) in an attempt to eliminate edema by the use of this strong solution of these salts. I have weighed all the hearts myself on the same scales and with as standard a technic as possible as to the time the tissues were kept on the weight pans, etc. Thirty per cent of the weight of the right ventricle has been deducted from that of the left, after the suggestion of Rytand and Dock,[23] to allow for the portion of the interventricular septum belonging to the right ventricle but weighed with the left. The resulting net weight of the left ventricle (L) is the numerator of the ratio L/W that expresses the relationship between the corrected weight of the left ventricle and the weight of the rat (W). It is usually between 0.3 and 0.6 Gm. for adult rats.

(The technical procedure for separating the ventricles from the auricles is relatively simple. The heart is removed from the rat's body by cutting all the great vessels as close to the heart as possible. Then, with the heart lying on its anterior surface, one blade of a sharp pair of scissors is inserted through the region of the coronary sinus and the incision continued around the heart between the right auricle and the right ventricle [following the right coronary vessels if these can be seen] and continued, always at right angles to the long axis of the heart, to the original incision. By this method, the ventricles are cleanly separated from the auricles and the roots of the aorta and the pulmonary artery. Both ventricles are then opened and sponged out. After being fixed over night in Kaiserling solution 1, the right ventricle is removed from the left by cutting the flange-like edge of the former flush with the interventricular septum.)

The denominator of this ratio, W, is the last weight of the rat, and for adults it is in the neighborhood of 200 to 400 Gm. The ratio is expressed as L in grams per hundred grams of W. Thus, for an animal with an L of 0.563 and a W of 244 the ratio is 0.563 divided by 2.44, or 0.23 per hundred grams of W.

If an animal was found during life or at autopsy to have a tumor or other condition, such as a galactocele, that would make a significant change in body weight, this rat was omitted from statistical consideration. Rats in several other categories were also omitted from consideration, namely, animals on which autopsies could not be made promptly, rats exposed to direct sunlight, rats treated with

21. Van Liere, E. S., and Sleeth, C. K.: Am. J. Physiol. **116**:635, 1936.

22. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938, p. 380.

23. Rytand, D. A., and Dock, W.: Arch. Int. Med. **56**:511, 1935.

2, 3-dimercapto-propanol N. N. R. (BAL, or British anti-Lewisite) in an unsuccessful attempt to remove silver with this substance[24] and rats subjected to renal "reduction."

SUMMARY OF RESULTS

After eliminating the animals mentioned in the foregoing paragraph there are 433 rats whose L/W ratios are open to no technical objection.

TABLE 1.—*Average L/W Values at Various Ages: Males**

Age, Months	Normal Lungs		Diseased Lungs	
	Silver	Water	Silver	Water
1	(3) .30 ± .04	(7) .25 ± .03	(2) .31 ± .05	.....
2	(6) .17 ± .01	(2) .17 ± .01	.....	.....
3- 5	(11) .19 ± .03	(8) .15 ± .01	(2) .18 ± .01	(1) .16
6- 8	(9) .14 ± .02	(5) .15 ± .01	(1) .19	(2) .18 ± .02
9-11	(10) .16 ± .02	(9) .15 ± .01	.....	(2) .17 ± .01
12-14	(16) .16 ± .01	(18) .16 ± .01	(7) .18 ± .03	(3) .22 ± .04
15-17	(11) .16 ± .01	(6) .16 ± .01	(2) .20 ± .04	(3) .17 ± .02
18-20	(11) .18 ± .01	(8) .16 ± .01	(7) .18 ± .03	(3) .19 ± .04
21-23	(7) .18 ± .02	(4) .16 ± .01	(5) .18 ± .02	(3) .16 ± .01
24-26	(3) .24 ± .04	.....	(5) .23 ± .04	.....
27-29	(9) .18 ± .03	.....	(2) .26 ± .08	.....
30-32	(1) .18	.....	(1) .26	.....
Unknown	.....	(5) .15 ± .01	.....	.....

* The figure in parentheses shows the number of rats in the group.

TABLE 2.—*Average L/W Values at Various Ages: Females**

Age, Months	Normal Lungs		Diseased Lungs	
	Silver	Water	Silver	Water
1	(2) .25 ± .03	(9) .25 ± .03	(2) .39 ± .03	.....
2	(7) .21 ± .05	(3) .16 ± .01	.....	(1) .34
3- 5	(7) .19 ± .02	(11) .18 ± .01	(1) .20	.....
6- 8	(6) .16 ± .02	(1) .17	.....	.....
9-11	(9) .19 ± .02	(13) .18 ± .01	(3) .15 ± 0	(1) .23
12-14	(14) .18 ± .02	(21) .18 ± .01	(2) .21 ± .07	(1) .18
15-17	(21) .20 ± .03	(7) .18 ± .02	(1) .20	(3) .22 ± .03
18-20	(11) .20 ± .02	(11) .19 ± .01	(5) .28 ± .03	(6) .24 ± .03
21-23	(13) .20 ± .03	(3) .20 ± .01	(1) .25	(2) .17 ± 0
24-26	(7) .22 ± .01	(2) .20 ± .03	.....	(1) .21
27-29	.....	(1) .17	(2) .25 ± .02	.....
Unknown	.....	(2) .18 ± .01	.....	.....

* The number in parentheses shows the number of rats in the group.

These 433 rats include 131 males given silver salts, 89 males given water, 114 females given silver salts and 99 females given water. The L/W values of these rats have been averaged according to age groups, and the

24. Olcott, C. T., and Riker, W. F., Jr.: Science **105**:67. 1937.

averages are listed in tables 1 and 2. The criteria by which normal and diseased lungs were differentiated will be considered in a later section.

Before a significant analysis of the L/W values can be made, a further elimination of animals is desirable:

1. It will be seen that among young rats both the water and the silver treated groups have high L/W values. These values are especially high among the youngest animals. Accordingly, 109 rats less than 9 months of age will be eliminated from further statistical study. This has the added advantage of removing rats that have received silver for only short periods.

2. Twenty-one male rats more than 24 months old which received silver but for which there were no control rats given water will be removed.

3. Seven rats of unknown age should be removed.

TABLE 3.—*Proportion of Rats Whose L/W Value Was More Than 0.2**

Age, Months	Normal Lungs		Diseased Lungs	
	Silver	Water	Silver	Water
		Males		
9-11	1/10	0/9	...	0/2
12-14	0/16	0/13	2/7	2/3
15-17	1/11	0/6	1/2	0/3
18-20	1/11	0/8	2/7	1/3
21-23	3/7	0/4	1/5	0/3
		Females		
9-11	3/9	2/13	0/3	1/1
12-14	1/14	4/21	1/3	0/1
15-17	9/21	1/7	1/1	2/3
18-20	6/11	2/11	5/5	5/6
21-23	5/13	2/3	1/1	0/2
24-26	7/7	1/2	...	1/1
27-29	....	0/1	2/2	...

* The numerator is the number of rats whose L/W value was more than 0.2; the denominator is the total number of rats in the age group.

The remaining 296 rats are represented in table 3 in such a way that the number of rats whose L/W was over 0.2 is placed as the numerator and the total number of rats in the group as the denominator.

Modification of Weight of Left Ventricle Caused by Pulmonary Lesions.—The lungs of 63 (21.2 per cent) of these 296 rats showed consolidation of one lobe or more and were thus considered to have a conspicuous and definite amount of pneumonia. (In one of these rats the pneumonia was less conspicuous, but there was purulent meningitis.) Twenty of these 63 rats died of natural causes, in contrast to only 6 of the 233 rats without significant pulmonary involvement. The results given in the tables conform with the experience of others who have found that bronchiectatic and pneumonic lesions increase with advancing

age.[25] Rats with diseased lungs tend to have higher L/W values than those with good lungs at the various ages. The L/W value tends to be higher for rats receiving silver than for those receiving water, whether or not they have diseased lungs.

Even more clearly shown is the greater variability of the average values of the L/W ratio in rats with diseased than in those with essentially normal lungs. This is apparent when it is noted in tables 1 and 2 that the average of the mean variation for most of the three month periods (the figure following the $\pm$ sign) is a relatively larger part of the average L/W value for that period (the figure before the $\pm$ sign) in rats with diseased lungs than in those with normal lungs. In the former it is often 1 : 5 or 1 : 6; in the latter it is usually in the neighborhood of 1 : 15 or 1 : 16.

Clear confirmation of the positive correlation between diseased lungs and relative hypertrophy of the left ventricle is given by the use of the "four-fold table."[26] This may be set up, including both silver-treated and water-treated rats, as follows:

a: 28 rats with L/W of 0.2 or more with diseased lungs
b: 35 rats with L/W less than 0.2 with diseased lungs
c: 49 rats with L/W of 0.2 or more with normal lungs
d: 184 rats with L/W less than 0.2 with normal lungs

Using the formula (chi = deviation [X] / standard deviation [6])

$$(\text{chi})^2 = \frac{(ad-bc)^2 \times (a+b+c+d)}{(a+b) \times (c+d) \times (a+c) \times (b+d)}$$

one obtains 3.76 as the value for chi, which is highly significant. To anticipate: This figure is higher than when the weight of the left ventricle is compared in rats given silver and rats given water. In other words, significant pulmonary disease is a more potent factor in causing a high L/W value than is the administration of silver. However, pulmonary changes do not give the uniformly high L/W values found for very young rats.

L/W Ratio in Rats with Normal Lungs.—To return to the tabulation of the L/W ratios and consider only the 233 rats (55 silver-treated and 45 water-treated males, 75 silver-treated and 58 water-treated females) with essentially normal lungs between 9 months of age and the end of the controls (between double lines on tables 1 and 2)—it will be seen that the average L/W value for male rats given water approximates 0.16, while that for females is rarely over 0.19. The L/W value for rats given silver, all ages and both sexes, is equal to or higher than that for rats given water. This higher value is usually due to increased

25. Saxton, J. A.: New York State J. Med. **41**:1095, 1941.

26. Hawley, P. R., in Simmons, J. S., and Gentzkow, C. J.: Laboratory Methods of the United States Army, ed. 5, Philadelphia, Lea & Febiger, 1944, p. 785.

weight of the left ventricle (L), as the body weights of the two groups show no consistent difference. In passing, it has been determined that the higher L/W values are not due to terminal loss of body weight.

In determining the value of chi for silver-treated rats in comparison with their controls, use has been made of the following diagram with the same 233 rats referred to in the foregoing paragraph:

(*a*) silver-treated rats with L/W of 0.2 or more	(*b*) silver-treated rats with L/W less than 0.2
(*c*) water-treated rats with L/W of 0.2 or more	(d) water-treated rats with L/W less than 0.2

For the 100 males	6	49	the chi is 2.29.
	0	45	
For the 133 females	31	44	the chi is 2.52.
	12	46	
For both sexes	37	93	the chi is 3.13.
	12	91	

The last-mentioned chi (3.13) is highly significant. as the probability of this figure occurring by accident is in the neighborhood of 1 : 400.

Relation of Elevation of L/W to Amount of Silver Received.—The 37 rats with L/W over 0.2 received more silver for a longer time and showed more silver on microscopic examination of their glomeruli than did the 93 rats with lower L/W values, as shown by the following scheme:

Of the 37 rats with L/W equal to or above 0.2 ↓		Of 93 rats with L/W less than 0.2 ↓
65%	received 11 Gm. of silver salts or more (there was a tendency for the rats given silver chloride to have a higher L/W value than those given silver nitrate)	42%
81%	received silver for 401 days or more	47%
95%	on microscopic examination showed 3 + or 4 + silver in their glomeruli	71%

L/W in Rats with Reduced Renal Parenchyma.—Two female rats (1 given silver, 1 given water) were subjected to unilateral nephrectomy and killed sixteen and nineteen months later. The values of L/W fitted into those of the series of rats with two kidneys.

Dr. William Dock "reduced" the kidneys of 10 of my rats by severely damaging one kidney with a clamp and removing its fellow a week or so later. The values of L/W when the animals were killed or died months later were: 0.32, 0.29, 0.25, 0.23 and 0.18 for 5 rats receiving silver and 0.29, 0.25, 0.24, 0.23 and 0.16, respectively, for 5 rats given water. These very high values were apparently largely due to an increase in L rather than to a decrease in W.

Possible Adventitious Change in L/W Ratio.—The question arises as to the possibility that the L/W values of rats given silver rose because silver was actually deposited in the heart. There is direct evidence that this is not the case: 1. The granules of silver found in the heart on microscopic examination were scattered, few and small. 2. Nitric acid digestion of the heart of a rat gave an entirely negative result for silver. Comparison of known amounts of silver nitrate indicated that if there was 1 mg. of silver in the entire heart its presence would be revealed by this test for silver. A trace of silver was recovered by digestion of renal and hepatic tissue.

It is of interest that no more vascular lesions were present in the kidneys of animals receiving silver than in those receiving water. There was no suggestion of necrosis or of significant thickening of the arterial walls.

Another possibility of error that must be eliminated is the possibility that the high L/W values might have been due to anemia, the latter caused by the ingestion of silver. In 19 determinations in rats given silver salts the hemoglobin was 14.6 ± 0.8 Gm., while in 12 determinations in rats given water, it was 15.1 ± 1.1 Gm.; i. e., no anemia was found. (The normal value for man in the Hellige colorimeter used is 14.6 Gm. per hundred cubic centimeters of blood.)

URINALYSIS

It is a well known fact that albuminuria is an apparently normal finding in old male rats.[27] When albumin was determined qualitatively with sodium sulfosalicylate in the urine of rats receiving silver and the urine of those receiving water, no clear difference was found.

Dr. Eyup Canat made a number of quantitative determinations of the protein in twenty-four hour urine samples from the rats. The results showed enormous variations. When repeated urinalyses were made there was shown a strong tendency for the proteinuria to increase through the months. Rats given silver had more proteinuria, on the average, than those given water. This may have been partly due to

27. Jackson, H., Jr., and Riggs, M. D.; J. Biol. Chem. **67**:101, 1926. Bell, M. E.: J. Physiol. **79**:191, 1933. Shih, H. E.: Am. J. Physiol. **113**:120, 1935. Saxton, J. A., Jr., and Kimball, G. C.: Arch. Path. **32**:951, 1941.

the greater age of the animals given silver. Males had slightly higher proteinuria than females. The figures may be rendered as follows:

Twenty-two determinations for silver-treated male rats 19 ± 6 months old gave a maximum of 368, a minimum of 1 and an average 83 ± 89 mg. of protein for 24 hours.

Four determinations for water-treated male rats 15± 4 months old gave a maximum of 18, a minimum of 1 and an average of 11 ± 6 mg. of protein per 24 hours.

Nine determinations for silver-treated female rats 14 ± 3 months old gave a maximum of 340, a minimum of 1 and an average of 75 ± 113 mg. per 24 hours.

Three determinations for water-treated female rats 12 ± 1 month old gave a maximum of 14, a minimum of 1 and an average of 9 ± 26 mg. per 24 hours.

Readings higher than any recorded in the foregoing paragraph were given by a water-treated male rat and a silver-treated male rat whose kidneys had been "reduced."

CREATININE

An attempt was made to get some light on the physiology of the kidney by determining the creatinine clearance. Unfortunately, presumably because of faulty collection, there were only negligible amounts of creatinine in the urine. The determinations of blood creatinine were apparently reliable. Three female littermates were killed when 16 months old. Analyses under the direction of Dr. Kendrick Hare, of the department of pediatrics, gave the following results:

2 rats given silver for 455 days:	0.54 mg. per 100 cc. blood
	0.68 mg. per 100 cc. blood
1 rat given water:	0.68 mg. per 100 cc. blood

Thus, in these animals there was no change in the retention of creatinine on the ingestion of silver.

COMMENT

This experiment was started after an examination of the slides from the case of argyria described by Gettler, Rhoads and Weiss [28] showed renal arteriosclerosis. Their patient was a moderately large man, about 70 years old, whose heart weighed 480 Gm. His blood pressure was not recorded. Kino [29] has been the only author to find significant arteriosclerosis in a patient with argyrosis, a man of 77 years. He main-

28. Gettler, A. O.; Rhoads, C. P., and Weiss, S.: Am. J. Path. 3:631, 1927.
29. Kino, F.: Frankfurt. Ztschr. f. Path. 3:398, 1909.

tained that silver pigmentation of the kidneys is primary, arteriosclerosis secondary. Hill and Pillsbury,[30] considering the condition in man, stated that "argyria . . . produces no significant disturbance of the physiology of the affected organs, or of the general health of the patient."

Silver nitrate or silver chloride held in suspension by sodium thiosulfate was given to many rats to see whether the ingestion of silver salts might cause vascular lesions. In a small number of rats the renal arteries of moderate size showed slightly thickened walls, but these changes were no more common in animals given silver than in those given water.

Although there has been no arteriosclerosis or other vascular change that could be attributed to silver, hypertrophy of the left ventricle has apparently been demonstrated in a statistically significant number of the animals treated with silver for long periods. Anemia was not present, and the increase in the weight of the heart was not due to its silver content. The most likely probability is that the ventricular hypertrophy indicated vascular hypertension.

The genesis of this presumed hypertension was not explained. Advanced pigmentation was present in the thyroid gland and in the medulla of the adrenal gland, but no change was found that is known to cause hypertension. The pigment deposited in the choroid membranes of the brain and the eye also seems to be an incidental finding. The most advanced pigmentation was present in the portal vein and the hepatic histiocytes, neither of which have any apparent connection with hypertension, and in the kidney. Changes in the kidney are known, from studies of man and animals, to be closely related to hypertension. Certainly our repetition of the work of many others who studied the influence of "reduced" kidneys has emphasized the likelihood of a renal factor in the hypertension. There may well have been a humoral mechanism associated with the pigmentation of the basement membrane of the renal tubules, but this cannot be proved or disproved. The possibility remains that changes in the structure of the heavily pigmented basement membranes of the glomeruli may have exerted some mechanical influence on the myocardium. It has been shown previously that these membranes were thickened.[1b] No article has been found describing such a change in the experimental work of others. However, the glomerular basement membranes are thickened in many cases of toxemia of pregnancy, and this thickening is accompanied by albuminuria and hypertension. It is submitted as a possibility that these same three

30. Hill, W. R., and Pillsbury, D. M.: Argyria: The Pharmacology of Silver, Baltimore, Williams & Wilkins Company, 1939, p. 132.

changes, thickened basement membrane, albuminuria and vascular hypertension, may have been present as interrelated factors in the animals ingesting silver.

SUMMARY

Hypertrophy of the left ventricle has been found in a statistically significant number of rats ingesting silver salts for long periods. This condition is presumed to indicate that they had vascular hypertension. It is postulated that the hypertension may have been due to the deposition of silver which produced thickening of the basement membranes of the renal glomeruli.