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ARTERY WALL ELECTROLYTES IN RENAL AND DCA HYPERTENSION¹

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PART I

Renal Hypertension

In an earlier study it was found that the renal artery of necropsied hypertensive subjects contained abnormally large amounts of sodium and water (1). The present study deals with the electrolyte composition of the aorta in rats with renal hypertension. After these aortas have been stripped of adventitia, at least two-fifths of the total area in tissue sections is occupied by smooth muscle cells. The remainder is largely connective tissue. The rat aorta thus provides for analysis a tissue rich in arterial smooth muscle. Moreover, the smooth muscle cells in the aorta are continuous with and have many of the pharmacological reactions of similar cells in the smaller arteries and arterioles (2). It seemed likely that any chemical alteration occurring in the aorta would give a clue to similar changes in the smooth muscle of arterioles. Technical difficulties have so far prevented us from analyzing the electrolyte content in the walls of arterioles.

METHODS

Hypertension was produced by compressing one kidney of 250 gm. male rats with a figure-of-eight ligature and removing the other kidney six days later. All the rats were fed rat chow³ (.3 per cent sodium and 1.2 per cent potassium) and water *ad lib*. Eight weeks or longer after the second operation, blood pressure was determined and the rats were sacrificed for tissue analysis.

The aortas were dissected, stripped of adventitia, blotted free of blood, and placed in weighing bottles. In one series of rats, tissues were dried, defatted, and extracted with 0.75N HNO₃ according to the method of Lowry and Hastings (3). Sodium and potassium concentrations

in the extract were determined with a Weichselbaum flame photometer. Chloride was determined by the potentiometric method of Kolthoff and Kuroda (4). In using this method, standard chloride solutions were used to bracket the unknown solutions. In another series of rats the tissues were dried and defatted as above, and extracted with 10 per cent trichloroacetic acid. Magnesium concentration was determined in this extract using the titan yellow method of Kunkel, Pearson, and Schweigert (5). Polyvinyl alcohol (Elvanol 51-05) was used to prevent precipitation of the MgOH-titan yellow complex.

Sera were analyzed for water, sodium, and potassium by the same methods. Blood urea was determined by a standard urease-nesslerization method.

Mean blood pressures were determined under ether anesthesia by direct puncture of the abdominal aorta below the level of the renal arteries. It was found that the depth of ether anesthesia could be varied considerably without changing the mean blood pressure. When the breathing of the rat indicated the proper plane of anesthesia, the blood pressure was read on the mercury manometer. This method gives very consistent results on normal rats. The average mean blood pressure of 26 normal rats was 106.7 mm. Hg with a standard deviation of only 8.4 mm. Hg.

All the normal unoperated rats had mean aortic blood pressures below 118 mm. Hg. Many of the rats underwent the kidney operations without ever developing significant hypertension. All operated rats with mean blood pressures below 121 mm. Hg were placed in the "operated normotensive" category. The average blood pressure of this group was 110 mm. Hg. Operated rats with mean blood pressures between 135 and 160 mm. Hg were considered to have moderate hypertension. Rats with mean blood pressures between 160 and 205 mm. Hg were classified as severely hypertensive.

RESULTS

With regard to sodium content (Table I), the aortas of the normal rats and the operated normotensives were not significantly different. However, the moderate hypertensive rats had a 6 per cent higher sodium content than the operated normotensives. The severe hypertensives had a 16 per cent higher sodium content than the operated normotensives. The differences between these three groups are significant.

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² This work was done during the tenure of an Established Investigatorship of the American Heart Association.

³ Obtained from Uncle Johnny Mills, Houston, Texas.

TABLE I
Sodium, potassium, and chloride content of the aorta
(mEq. per 100 gm. of dry fat-free aorta solids)

Groups of rats	No. of rats	Total Na*	Calculated extracellular Na*	Total Cl*	Total K*
Severe hypertensives	5	39.6 ± .9	34.2	25.4 ± .8	13.5 ± .6
Moderate hypertensives	11	36.2 ± .7	32.3	24.7 ± .4	11.3 ± .4
Operated normotensives	16	34.2 ± .7	32.5	26.0 ± .4	11.4 ± .3
Normal rats	12	35.8 ± .5	31.5	25.4 ± .9	9.5 ± .1
DCA hypertensives	6	43.5 ± 1.5	34.3	26.8 ± .4	10.9 ± .4

* Group mean.

± indicates standard error of the mean.

The chloride content of the aortas (Table I) was not significantly abnormal in any of these groups. Moreover, the chloride concentration in plasma was fairly similar for all groups. If one assumes that all of the chloride in the aorta is in the extracellular fluid in the same concentration as in an ultrafiltrate of plasma, then the amount of extracellular fluid and extracellular sodium in these aortas per 100 gm. of dry fat-free solids can be calculated by the method of Hastings and Eichelberger (6). The calculated extracellular fluid per 100 gm. of aorta solids is 228.5 gm. in the operated normotensive rats, 224.8 gm. in the moderate hypertensive group, and 234.8 gm. in the severe hypertensive group. The calculated extracellular sodium per 100 gm. of dry solids is 32.5 mEq. in the operated normotensive rats, 32.3 mEq. in the moderate hypertensive rats, and 34.2 mEq. in the severely hypertensive rats (Table I). From these calculations, it is seen that the increased Na concentration in the aortas of the moderate hypertensive rats compared to the operated normotensive rats cannot be explained even in part as an increased in extracellular sodium. The aortas from the severely hypertensive rats do have 1.7 more milliequivalents of calculated extracellular sodium per 100 gm. of solids when compared to the aortas

of operated normotensive rats. However, this increase in calculated extracellular sodium accounts for only 31 per cent of the total increase in sodium content present in the aortas of the severely hypertensive rats when compared with the operated normotensive group. Considering these calculations, it seems unlikely that the increased sodium concentration in the aortas of the hypertensive rats is explainable as an increase in the proportion of extracellular fluid.

TABLE II
Magnesium content of aorta
(mEq. per 100 gm. of dry fat-free solids)

	No. of rats	Group mean ± S.E. of the mean
Normal rats	8	4.61 ± .19
Operated normotensives	10	4.33 ± .16
Hypertensives	14	4.02 ± .12

The aorta potassium content (Table I) in the operated normotensive rats was 20 per cent higher than that present in the aortas of normal rats. The moderate hypertensive group showed about this same value. The severe hypertensive group had an aorta potassium content 18 per cent above that in the operated normotensive group. These differences are highly significant.

TABLE III
Serum concentrations of sodium, potassium, and chloride in milliequivalents per liter of serum

	No. of rats	Na*	K*	Cl*
Severe hypertensives	5	145.7 ± 2.3	6.9 ± .7	98.6 ± 1.4
Moderate hypertensives	11	143.7 ± 1.3	5.9 ± .4	104.7 ± .6
Operated normotensives	16	142.3 ± .8	6.2 ± .15	103.5 ± .5
Normal rats	12	143.1 ± 1.0	5.7 ± .2	105.1 ± .8
DCA hypertensives	6	145.5 ± 1.3	4.3 ± .2	103.6 ± 1.7

* Group mean.

± indicates standard error of the mean.

Table II shows the results of magnesium analyses on the aortas in a smaller series of rats. All hypertensive rats were combined in one group with an average blood pressure of 145 mm. Hg. Blood pressures in this group ranged from 127 to 205 mm. Hg. The aortas in this hypertensive group showed a magnesium content 13 per cent lower than normal, a significant difference. The severe hypertensives were no lower than moderate hypertensives.

These changes in the aortas of hypertensive rats occurred whether or not azotemia was present.

Table III gives the average serum concentrations for sodium, chloride, and potassium. The severe hypertensives show some increase in serum potassium concentration as well as a 6 per cent decrease in chloride concentration. The lowered chloride concentration is probably due in the main to uremic acidosis in two of the rats in this group.

DISCUSSION

These data indicate that the composition of the aorta becomes altered in rats with renal hypertension. The changes in the aorta are fairly specific in that brain and muscle tissue in the same rats showed relatively insignificant changes in sodium, potassium, or magnesium composition that can be correlated with hypertension (7). Moreover, the increased sodium concentration in the aortas of the hypertensive rats cannot be accounted for merely as an increase in the proportion of extracellular fluid, as mentioned. The intracellular compartment (mainly vascular smooth muscle cells) remains the most likely part of the aorta responsible for the observed changes in composition that are related to hypertension.

The fact that the potassium content increased while Mg content decreased in the aortas from hypertensive rats is unusual for muscle tissues. In skeletal muscle the ratio of these two important intracellular cations usually remains constant even under quite varying conditions (8).

We are unable to say whether or not these chemical abnormalities of the aorta play an important role in the pathogenesis of renal hypertension. However, there are several interesting relationships which suggest that they might.

The changes in the composition of the aorta associated with hypertension may be fundamentally

related to the hypertensive process in a causal way or may be a result of the hypertension. An increase in lateral pressure in the aorta associated with hypertension would have the effect of ultra-filtering more extracellular fluid into the aorta wall. However, the rate of egress of this fluid into the capillaries and lymphatics of the adventitia seems to keep pace with the faster introduction of fluid, since there is no sizeable increase in the proportion of extracellular fluid in the aortas of hypertensive rats. Moreover, we have measured the water content in the aorta tissue above and below a coarctation of the aorta in five human cases, and the upper segment which is under a higher arterial pressure has the same water content as the lower segment.

The compositional changes in the aorta might be the result of a contraction of smooth muscle cells. This possibility is under investigation at the present time. Depolarization may induce electrolyte changes in these cells which in turn influence the state of contraction of actomyosin. It is also possible that the compositional changes in the aorta instead of resulting from smooth muscle contraction may either make the muscle cells more sensitive to depolarization or might induce a stronger contraction for a given degree of depolarization. Whatever mechanism is operating, the altered composition of electrolytes could conceivably have important effects on the tension of arterial smooth muscle. First, if total intracellular cation concentrations were altered, there would be changes in the membrane potential. Such changes in membrane potential have an important influence on actomyosin kinetics. It has been shown in the frog heart that a high membrane potential tends to keep the actomyosin uncontracted. Conversely, a lowered membrane potential favors contraction (9). It has also been shown that arterial strips with a lowered membrane potential are more sensitive to nor-epinephrine (2).

Secondly, it is an equally pertinent observation that actomyosin-ATP kinetics in all types of muscle are markedly influenced by the intracellular ionic environment. As little as a 3 per cent change in ion composition can mean the difference between an actomyosin contraction with maximal tension and a contraction that develops no tension (9). The amount of intracellular potassium and sodium ions in relation to intracellular solids is more im-

portant to the development of tension than the concentration of these ions in intracellular water (9). Intracellular magnesium ion content is also highly important in relation to the contraction of actomyosin as well as to its relaxation (10, 11).

Such an effect of the ions on smooth muscle membrane or actomyosin may account for Wiggers' observation that the large arteries in hypertensive patients showed a definite decrease in elasticity even in the absence of atherosclerosis or old age (12).

It is known that diets low in either sodium or potassium cause a reduction in blood pressure in rats with renal hypertension (13, 14). These dietary effects are also present in hypertensive man (15, 16). It is possible that these diets lower blood pressure by reducing the elevated sodium or potassium in the arteries of hypertensives to a more normal level. This possibility is now under investigation.

It is not known whether adrenal cortical hormones participate in the arterial electrolyte changes associated with renal hypertension. In another part of this study, it was found that the aortas of rats with DCA hypertension show significant increases in sodium and potassium concentration, a pattern similar to that seen in the aortas of rats with renal hypertension.

As seen in the "operated normotensive" group, renal damage resulting from the operation evidently can produce an elevation of potassium concentration in the aorta, part of the chemical "lesion" of hypertension, without causing a significant rise of the blood pressure. This elevation was not necessarily associated with azotemia since it occurred in operated normotensive rats with a normal blood urea nitrogen level.

PART II

Desoxycorticosterone Hypertension

Large doses of desoxycorticosterone acetate (DCA) in combination with a high sodium intake will produce hypertension in man as well as in many lower mammals. This rise in blood pressure can be completely prevented by diets very low in sodium (17) or potassium (18) content. The hypertension accompanying DCA is increasingly severe as larger amounts of sodium are included in the diet. In view of the great influence of

dietary sodium and potassium on this type of hypertension, it seemed of interest to determine the sodium and potassium concentrations of arteries in DCA hypertensive rats and compare them with the findings in normal rats.

METHODS

Hypertension due to DCA was produced in 250 gm. male rats by injecting subcutaneously 5 mgm. of DCA ("Percorten")⁴ every day for six weeks. During this period the rats were allowed to drink only a 1 per cent NaCl solution. There were no operations or manipulations involving the kidney. During the entire injection period, the rats appeared healthy and active. At the end of the six week injection period, the rats were exsanguinated and samples of aorta, cerebrum, and hamstring muscles were obtained for chemical analysis. The aortas were stripped of adventitia, and as much connective tissue as possible was trimmed from the skeletal muscle samples prior to analysis.

Methods for determining blood pressure and for the chemical analyses are described in Part I of this paper. Chloride in brain and muscle was determined by the Volhard method (3). A blood pressure of 124 mm. Hg is two standard deviations above the mean for the normal rats. Any blood pressure above this level was considered hypertensive. The six rats which developed DCA hypertension had blood pressures ranging from 125 to 158 mm. Hg with a group average of 136 mm. Hg. These rats were compared with the group of normal rats similar in age and sex mentioned in Part I of this paper. Both normal and hypertensive rats were fed a rat chow containing .3 per cent sodium and 1.2 per cent potassium. The normal rats were allowed to drink water *ad lib*.

RESULTS AND DISCUSSION

The content of sodium and potassium in the aortas is given in Table I. The aortas of the DCA hypertensive rats had a 22 per cent greater sodium content and a 15 per cent greater potassium content (per 100 gm. DFFS) than the aortas of normal rats. These differences are statistically significant.

The DCA hypertensive aortas also had a 5 per cent greater chloride concentration, but this was not a significant difference.

Table III shows the serum concentrations of Na, K, and Cl in the normal and DCA hypertensive rats. As would be expected from many reports the DCA hypertensives have a slightly higher than

⁴ Percorten was kindly furnished by Dr. Ernst Oppenheimer of the Ciba Pharmaceutical Company.

normal serum sodium concentration and a lower potassium and chloride concentration.

If one assumes that all the chloride in the aorta is in the extracellular fluid, then one can calculate the amount of extracellular fluid and extracellular sodium per 100 gm. of dry fat-free solids using the system of Hastings and Eichelberger (6). In the aortas of DCA hypertensive rats there were 236 gm. of extracellular fluid per 100 gm. of solids compared to 220 gm. in the normal aortas. The aortas of the DCA rats had a calculated 34.3 mEq. of extracellular sodium per 100 gm. of dry solids, compared to 31.5 mEq. of extracellular Na in the normal aortas (Table I). The DCA hypertensive aortas had 7.7 more mEq. of total Na per 100 gm. of solids than the normal aortas; 2.9 of these extra milliequivalents can be explained by an increase in extracellular Na in the DCA aortas. The other 4.8 mEq. of increased sodium content in the DCA aortas is probably an increase in intracellular sodium.

The implications of altered intracellular sodium and potassium with respect to the tonus of arterial smooth muscle have been discussed in Part I of this paper.

It is of interest that the concentrations of sodium and potassium in the aorta are increased in both renal and DCA hypertension. It is too early to tell whether this pattern is a fundamental chemical "lesion" that accompanies all types of experimental hypertension in the rat.

PART III

Comparison of the Electrolyte Changes in Artery, Brain, and Skeletal Muscle Produced by Desoxycorticosterone and Salt

After the administration of large doses of desoxycorticosterone acetate (DCA) in conjunction with a large sodium intake, most mammals show a positive sodium balance and a negative potassium balance. This is reflected in slight increases in serum sodium concentration and decreases in serum potassium concentration. It is also reflected in an increased sodium concentration and a decreased potassium concentration in skeletal muscle (19). It is not clear, however, that tissues other than skeletal muscle behave in a similar manner. This is especially important in regard to arteries, inasmuch as the compositional changes in skeletal

muscle induced by DCA have been assumed to occur in the arteries as well. The changes in the electrolyte composition of brain, skeletal muscle, and aorta under the influence of DCA and salt were therefore studied to determine to what extent the responses of different tissues are the same as those of skeletal muscle. These analyses were carried out on the rats made hypertensive with DCA as well as the normal control rats that are described in Part II of this paper.

RESULTS AND DISCUSSION

The tissue composition of skeletal muscle in the DCA treated rats is presented in Table IV. Confirming previous reports, the sodium content of muscle increased from 8.2 mEq. (per 100 gm. DFFS) in the normal group to 14.1 mEq. in the DCA group while the potassium content dropped from 47.5 mEq. (per 100 gm. DFFS) in the normal group to 39.5 mEq. in the DCA group. The chloride content of skeletal muscle rose from 4.1 mEq. per 100 gm. DFFS in the normal rats to 5.0 mEq. in the DCA rats. These differences are highly significant. The water content was almost exactly the same in the two groups.

Assuming that all the chloride in whole skeletal muscle is in the extracellular phase at the same concentration as in an ultrafiltrate of plasma, the partition of water, sodium, and potassium between the extracellular and intracellular phases can be estimated using the methods of Hastings and Eichelberger (6). The intracellular phase lost 8 mEq. of potassium per 100 gm. DFFS while gaining 4.6 mEq. of sodium. In terms of concentration per liter of cell water, sodium increased 17 mEq. per liter above normal and potassium fell 24.3 mEq. per liter below normal in the DCA rats (Table IV).

Analysis of brain in the DCA group gave somewhat different results (Table V). The mEq. of sodium per 100 gm. DFFS increased from 23.9 in the normal rats to 25.4 in the rats receiving salt and DCA. Chloride (per 100 gm. DFFS) also increased from 21.2 mEq. in the normal rats to 21.8 mEq. in the DCA group. This is a much smaller increase in sodium than occurred in skeletal muscle. Furthermore, the brain potassium content per 100 gm. DFFS increased 10 per cent above normal in the DCA rats instead of showing

TABLE IV
Water and electrolyte composition of skeletal muscle*

	No. of rats	Direct data				Derived data					
		Na ⁺ † (mEq.)	K ⁺ † (mEq.)	Cl ⁻ † (mEq.)	H ₂ O _T † (gm.)	H ₂ O _E † (gm.)	H ₂ O _I † (gm.)	(Na) ⁺ † (mEq.)	(K) ⁺ † (mEq.)	[Na] _I † (mEq.)	[K] _I † (mEq.)
Normal rats	12	8.2±.15	47.5±.9	4.1±.1	318.4±4.2	35.6	282.8	3.1	47.3	11.0	167.5
DCA treated rats	6	14.1±.5	39.5±.8	5.0±.1	318.8±1.9	44.0	274.8	7.7	39.3	28.0	143.2
% difference		+72%	-17%	+22%	+1%	+24%	-3%	+148%	-17%	+155%	-14.5%
p value		<.001	<.001	<.001	.9						

* ± indicates standard error of the mean.

H₂O_T total water per 100 gm. of dry fat-free muscle solids.

H₂O_E extracellular water per 100 gm. of dry fat-free muscle solids.

H₂O_I intracellular water per 100 gm. of dry fat-free muscle solids.

()_I mEq. of intracellular cation per 100 gm. of dry fat-free muscle solids.

[]_I mEq. of intracellular cation per Kg. of cell water.

† Per 100 gm. of dry fat-free muscle solids.

the decrease that is characteristic of skeletal muscle. The DCA group had an average of 51.8 mEq. of potassium per 100 gm. of DFFS compared to 47.1 mEq. in the normal group. All these differences between the normal and DCA groups were statistically significant. Water content was not significantly different in the two groups.

If the "chloride space" calculations are applied to brain in the same manner as was used with skeletal muscle, negative values for intracellular sodium are obtained. This is probably explained by the fact that brain cells are bathed by a fluid with the composition of cerebrospinal fluid rather than an ultrafiltrate of plasma. The concentration of chloride in cerebrospinal fluid exceeds that in an ultrafiltrate of plasma by about 12 mEq. per liter. Using this assumption the partition of water, sodium, and potassium between extra- and intracellular phases has been calculated and is shown in Table V. The calculations are the same as those applied to skeletal muscle except that the

concentration of chloride in brain extracellular fluid was assumed to be 12 mEq. per liter more than in an ultrafiltrate of plasma. By these methods, the calculated intracellular sodium is zero in normal brain tissue and it increases by an insignificant amount (.06 mEq. per 100 gm. DFFS) in the brain tissue of the DCA group. The intracellular potassium of brain per 100 gm. DFFS increases 10 per cent above normal. Thus the intracellular phase in the DCA rats gains 4.8 mEq. of potassium per 100 gm. DFFS and keeps about the same content of sodium, while losing 7.6 gm. of water. Consequently, the calculated concentration of potassium per Kg. of brain cell water increases from 119 mEq. per Kg. in the normal group to 134 mEq. per Kg. in the DCA group.

As mentioned in Part II of this paper, the aorta shows still another pattern of change under the influence of DCA and salt. In the aorta both sodium and potassium (per 100 gm. DFFS) are increased above normal levels in the DCA group.

TABLE V
Water and electrolyte composition of brain*

	No. of rats	Direct data				Derived data					
		Na ⁺ † (mEq.)	K ⁺ † (mEq.)	Cl ⁻ † (mEq.)	H ₂ O _T † (gm.)	H ₂ O _E † (gm.)	H ₂ O _I † (gm.)	(Na) ⁺ † (mEq.)	(K) ⁺ † (mEq.)	[Na] _I † (mEq.)	[K] _I † (mEq.)
Normal rats	12	23.9 ±.3	47.1±1.0	21.2±.2	555.6±3.0	166.8	388.8	0	46.3	0	119.0
DCA rats	6	25.35±.7	51.8±1.2	21.8±.2	555.0±4.5	173.8	381.2	.06	51.1	0.16	134.0
% difference		+6%	+10%	+3%	-.1%	+4%	-2%		+10%		+13%
p value		.04	<.001	.02	.9						

* ± indicates standard error of the mean.

H₂O_T total water per 100 gm. of dry fat-free brain solids.

H₂O_E extracellular water per 100 gm. of dry fat-free brain solids.

H₂O_I intracellular water per 100 gm. of dry fat-free brain solids.

()_I mEq. of intracellular cation per 100 gm. of dry fat-free brain solids.

[]_I mEq. of intracellular cation per Kg. of cell water.

† Per 100 gm. of dry fat-free brain solids.

The results reveal that large doses of DCA combined with a high sodium intake produce considerable alterations in tissue electrolyte concentrations. The most significant conclusion, however, is that the various tissues do not respond in like manner to the administration of DCA and salt. Skeletal muscle fibers gain in sodium and lose potassium. Brain cells gain considerable potassium while gaining only insignificant amounts of sodium. The smooth muscle of the aorta gains not only potassium but sodium as well. Thus there is no uniform biological response of all types of cells to DCA administration, and each type of tissue cell must be considered separately.

This is also true for cortisone. Streeten and Solomon have found increases in the potassium concentration of red cells after cortisone administration (20), while Seldin, Welt, and Cort have shown that potassium concentration in skeletal muscle decreases under the influence of cortisone (21).

In regard to DCA hypertension, these results indicate that one cannot make valid inferences concerning the effect of DCA and salt on the electrolyte composition of arteries by analyzing skeletal muscle.

SUMMARY OF PARTS I, II, AND III

1. The aortas of rats with renal hypertension have both a higher sodium and a higher potassium concentration than the aortas of rats which have undergone the same type of kidney operation but remain normotensive.

2. The aortas of these "operated normotensive" rats have a higher potassium concentration than the aortas of normal rats.

3. In a smaller series of rats, the aortas of renal hypertensive rats have a 13 per cent lower magnesium concentration than normal rats.

4. The aortas of DCA hypertensive rats also have both a higher sodium and a higher potassium concentration than seen in normal aortas. Thus, the aortas have the same type of chemical alterations in both renal and DCA hypertension.

5. From calculations of "chloride space," no more than a third of the increased sodium concentrations in the hypertensive aortas can be explained as an increase in extracellular sodium.

6. DCA greatly increases sodium and decreases potassium concentration in rat skeletal muscle.

DCA causes a slight increase in brain sodium concentration, but produces a considerable increase in brain potassium concentration. DCA effects a considerable increase in both sodium and potassium concentration in rat aorta.

7. Thus, with regard to electrolyte composition, there is no uniform biological response in all types of cells to DCA administration. Each type of tissue cell must be considered separately.

8. Inferences concerning the electrolyte composition of arteries in DCA hypertension cannot be made from analyses of skeletal muscle.

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