parently enhanced the susceptibility of Rh cells to DA virus and made it possible to recognize the infection more readily by the presence of multinucleated giant cells in stained preparations. These findings suggest the possibility that DA virus might promote cell division in x-irradiated cells during the early phases of infection, such as is observed in human kidney cells infected with croup-associated virus(12). Since x-irradiation induces mononucleated giant cells in uninfected cultures, it is conceivable that the walls of such cells are more delicate and subject to lysis by DA virus. Both processes, that is, rapid cell division and fusion of infected cells, could occur simultaneously in the irradiated, infected cultures resulting eventually in a high percentage of multinucleated giant cells. Regardless of the mechanism involved in formation of syncytial cells in the infected irradiated cultures, x-rays apparently produce changes only when the cell system is not totally resistant to infection with a given virus. Thus, with DA virus, which multiplied well in Rh cells, cytopathology of infected cells could be enhanced by exposing cultures to x-rays; however, this exposure must take place during the *early* phases of growth.

Summary. Rhesus monkey kidney cells were found to be capable of forming a uniform monolayer even though they were highly infected with DA, a myxovirus. Irradiation did not result in readily observable CPE in virus infected cultures, although examination of stained preparations revealed definite changes as compared with control cultures. Increased numbers of multinucleated giant cells were observed in infected cultures exposed to x-rays, whereas considerably fewer and only mononucleated giant cells were obtained in irradiated cells without virus infection.

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Mechanism of Anti-Hypertensive Action of Thiazides.* (28155)

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The basis for the anti-hypertensive action of chlorothiazide or its derivatives remains obscure. The preliminary explanations that blood pressure is depressed through loss of sodium or reduction of plasma volume have been, generally, discounted. These mechanisms seem even more untenable in view of the recent demonstration that a benzothiadiazine analogue, diazoxide (7-chloro-3-methyl-1, 2, 4-benzothiadiazine-1, 1-dioxide), has a potent anti-hypertensive effect in the absence of diuresis(1).

It seemed worthwhile, however, to examine the possibility that diazoxide might alter the aorta wall electrolytes of hypertensive rats. This investigation seemed pertinent in view

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TABLE I. Concentration of Aorta Electrolytes and Water.*

	No. rats	Avg B.P. (mm Hg)	H_2O (g)	Cl (meq)	Na (meq)	K (meq)	
Normal	18	116 (96-122)	192 ± 1.3†	19.9 ± .21	24.8 ± .36	11.5 ± .14	
Hypertensive	18	192 (166-220)	241 ± 2.4	24.5 ± .42	31.7 ± .66	15.1 ± .31	
Hypertensive + diazoxide	14	140 (118-156)	231 ± 2.1	23.2 ± .31	30.2 ± .57	12.8 ± .22	$P < .01$
Normal + diazoxide	8	108 (94-118)	196 ± 1.4	20.1 ± .26	25.2 ± .30	11.4 ± .23	

* Per 100 g fat-free dry wt. † Standard deviation.

TABLE II. Distribution of Electrolytes and Water in Aorta Wall.*

	H_2O (g)		Na (mEq)		K (mEq)	
	Extra-cell	Intra-cell	Extra-cell	Intra-cell	Intra-cell	
Normal	18.0 ± .4	174 ± 1.0	23.4 ± .31†	1.4 ± .08	11.0 ± .13	
Hypertensize	22.9 ± .9	218 ± 1.6	28.8 ± .64	2.9 ± .10	14.6 ± .30	
Hypertensive + diazoxide	20.9 ± .7	210 ± 1.8	27.1 ± .51	3.1 ± .11	12.3 ± .21	$P<.01$
Normal + diazoxide	18.0 ± .3	178 ± 1.3	23.5 ± .29	1.7 ± .07	10.9 ± .22	

* Per 100 g fat-free dry wt. † Standard deviation.

of previous demonstrations from this laboratary that, under several conditions, the blood pressure level parallels the potassium content of the aorta wall of rats(2).

Methods. Five- to 6-week-old Long-Evans male rats were subjected to Grollman's figures-of-eight renal ligation method of inducing hypertension. Ten weeks later a group of such rats, with systolic blood pressures averaging 192 mm Hg, were fed a stock diet incorporating diazoxide† estimated to provide a daily intake of approximately 30 mg/kilo of body weight. After 2 weeks the blood pressures had declined to an average of 140 mm Hg. The rats were then sacrificed. The aortas were rapidly removed, stripped of adventitia, and weighed, then oven-dried at 100°C, extracted with ether to remove the fat, and the residue weighed to obtain the water content. The dried tissue was then digested in 0.75N nitric acid and assayed for chloride by the Cotlove amperometric method and for sodium and potassium by flame photometry.

The following groups of rats were subjected to the same procedure: (1) hypertensive rats on stock diet; (2) normal rats on stock diet; and (3) normal rats on the diet containing diazoxide for 2 weeks. Blood was obtained from all groups for similar electrolyte analyses of the serum.

Results. Table I contains the results of analyses of the aortas of the 4 groups of rats. Ingestion of diazoxide by normal rats had no appreciable effect on blood pressure or on water, chloride, sodium and potassium contents of the aorta wall. Also, the aortas of untreated hypertensive animals contained an approximate 20% increase in water, chloride and sodium and about 30% in potassium. The aortas of hypertensive rats ingesting diazoxide had similar values for water, chloride and sodium. However, potassium concentration of these aortas was decreased from hypertensive levels of 30% above normal to 10% above normal.

Concentration of chloride, sodium and potassium in the sera of all 4 groups was practically identical, namely, chloride—106 ± 0.9 meq/l, sodium—142 ± 0.7 meq/l, and potassium—5.1 ± 0.1 meq/l.

The data in Table I were then subjected to calculations using standard formulae to determine the distribution of water, sodium, and potassium between the intra- and extracellular compartments of aorta tissue (Table II). Diazoxide ingestion by normal rats had no effect on the distribution of these constituents in the aorta wall. Distribution of water and

† Supplied by Schering Corp., Bloomfield, N. J., through the courtesy of Dr. Alan A. Rubin.

sodium in the aortas of hypertensive rats was unchanged by diazoxide treatment. However, treatment with this compound caused a reduction in intracellular concentration of potassium of about 15%.

Discussion. Data published previously from this laboratory have indicated that, under a number of conditions, changes in blood pressure parallel the concentrations of potassium of arterial tissue. Tobian has agreed that there is an excellent correlation between blood pressure values and aorta potassium content(3). The present experiment offers additional evidence of this relationship by demonstrating that diazoxide treatment, which lowers the blood pressure of hypertensive rats, is associated with a decrease in intracellular potassium concentration of the aorta and appears to have no effect on water or sodium distribution.

It has been suggested that diazoxide exerts its anti-hypertensive effect by directly influencing arterial smooth muscle contraction. This concept is based in part on the fact that this substance suppresses the arterial contractions induced by pressor agents. It is significant that a decrease in peripheral vascular response to pressor agents was obtained in rats whose aorta potassium content was reduced by dietary measures(4). It is therefore possible that diazoxide may influence arterial muscle contraction through its effect on lowering intracellular potassium content.

It is suggested that the anti-hypertensive action of chlorothiazide or derivatives is also mediated through the change in potassium content in arterial smooth muscle, in view of (1) the chemical relationship to diazoxide, (2) similar suppression of vascular response to pressor agents, and (3) partial restoration of blood pressure following administration of supplemental potassium(5).

The present experimental data offer an opportunity to clarify the role of "water-logging" in the mechanism of hypertension. It has been claimed that the increased water content found in the arteries of hypertensive animals induces an increased peripheral vascular resistance through the passive narrowing of the arterial lumen. It is now disclosed, that diazoxide lowers the blood pressure of hypertensive rats without reducing the water content of either the extracellular or intracellular compartments of aorta tissue. It appears, therefore, that increased hydration of arterial tissue *per se* is incapable of maintaining hypertension. Thus it is questionable that it plays a role in the etiology of blood pressure elevation.

Summary. The non-diuretic thiazide, diazoxide, lowers blood pressure of renal hypertensive rats in association with a decrease in aorta wall potassium content. At the same time, sodium and water concentration and their distribution in the tissue compartments of the aortas of such rats remain unchanged. It is suggested that the anti-hypertensive effect of thiazides is mediated through the reduction in potassium concentration of arterial smooth muscle.

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