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Some Problems in Diuresis

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SOME PROBLEMS IN DIURESIS

by

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LIFE

James Wendell Flesher was born in Chicago, Illinois on June 24, 1925.

He graduated from Morgan Park High School, Chicago, Illinois, June 1943. In July, 1943, he enlisted in the United States Army as a private. Selected for the Aviation Cadet Training Program, he was sent to the University of Alabama for Pre-Flight Training. Upon completion of this training he was transferred, due to the urgency of the European Conflict, to the 65th Infantry Division.

He was sent to France in December, 1944 where he served as a rifleman in General Patton's Third Army. He remained with the 65th Division in the campaign to conquer Central Europe.

After V-E day he was assigned as Information and Education representative for the batallion. In this capacity he presented short talks each week to the men of the batallion concerning occupation policies, current events, and educational opportunities. He attended the newly formed Biarritz American University from January to April, 1946. He was honorably discharged for the U.S. Army in April, 1946.

From June, 1946 until June 1949 he attended Northwestern University. In June, 1949 he received the degree of Bachelor of Science with majors in Chemistry and Biology. He

attended the Graduate School of the University of Illinois from September, 1949 until March 1950, when he accepted a technical position with the Institute of Radiobiology and Biophysics of the University of Chicago. While with the Institute he worked on the problem of the conduction of the nerve impulse in the giant axon of the squid, at the Marine Biological Laboratory, Woods Hole, Massachusetts.

In February, 1951 he accepted a position as a chemist in the Edible Fats and Oils Division of Lever Brothers Company, Hammond, Indiana, a position which he still holds.

In September, 1951, he began his studies at Loyola University.

In August, of 1952, he married Ilga Brauers.

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CHAPTER I

INTRODUCTION

This study concerns the investigation of some diuretic problems dealing with the action of several compounds on urine and electrolyte output. A brief literature survey follows for these compounds: arterenol, salyrgan, dextrose, and sorbitol.

Arterenol

The availability of pure l-epinephrine and l-norepinephrine (arterenol), has created new interest in the problem of the relation of the adrenal medullary hormones to diuresis. The older literature concerned itself with the action of the impure mixture of adrenal medullary hormones called "epinephrine" on kidney function. Goldenberg et al (1949), has shown "epinephrine" to be two distinct hormones, now called l-epinephrine and l-norepinephrine.

Previous work centered around the prediction by Starling (1918), that the rate of glomerular filtration might be affected by the relative calibers of the afferent and efferent arterioles. Ten years later, Richards and Plant (1928), observed a diuresis in the dog and rabbit, and attributed it to vas efferens constriction with a consequent rise in glomerular filtration pressure. Further studies on urine flow in the dog after

epinephrine (Winton, 1931; Toth, 1937), showed that small doses produced polyuria, large doses oliguria. This action was interpreted as due to a change in the glomerular filtration rate. In the guinea pig however large amounts of epinephrine (up to 500 ug./kg.) greatly increased the water and salt excretion to 50 to 60% higher than the controls (Kroneberg and Ocklitz, 1949).

The introduction of renal clearance techniques failed to substantiate the inferences of those who believed that epinephrine increased the glomerular filtration rate in man or in the dog (Smith, 1951; Chasis et al, 1951; Hough, 1951; Ranges et al, 1943). Pickford and Watt (1951), however, feel that, in general, the renal plasma flow and the glomerular filtration rate run parallel with the rate of urine flow. The literature of the mechanism of action of epinephrine on urine flow appears controversial.

The recent literature concerns itself with the action of the pure hormones, l-epinephrine and l-norepinephrine. Harris et al (1950) and Eversole et al (1952), have pointed out that in the rat, the diuretic effect of the adrenal medullary hormones is due to the activity of l-norepinephrine and that pure l-epinephrine does not stimulate water diuresis. L-norepinephrine acts according to these workers, by increasing the excretion of sodium chloride, which has an osmotic action in the tubules, and by increasing the glomerular filtration rate as measured by creatinine.

Drill and Eristol (1951) however, found l-epinephrine, as well as l-norepinephrine produced diuresis in rats. The chloride excretion was also increased in these animals. Glomerular filtration rate was not studied. Haltz et al (1947), also found l-epinephrine and l-norepinephrine produced similar effects in the guinea pig, as well as in the rat.

In the dog, Dearborn and Lasagna (1952), and Franko and KarVonen (1952), reported antidiuretic effect elicited by both l-epinephrine and l-norepinephrine in doses of 3 to 30 ug./kg. i.v. Both studies divided the antidiuresis into two phases: A short effect of the same duration as changes in the glomerular filtration rate, and a long effect which persists after the circulation has returned to normal. The long antidiuretic effect was attributed to the release of the antidiuretic hormone since it could not be elicited in dogs whose hypothalamo-hypophyseal system was surgically damaged.

Kaplan et al (1952), found only slight and inconstant alterations in renal plasma flow, glomerular filtration rate and sodium and chloride excretion in the hydropenic dog during mannitol diuresis. The urine output was similarly inconstant. In these experiments l-norepinephrine was given at the rate of 0.07 ug./kg./ min. to 1.4 ug./kg./ min. Leimdorfer (1953), found l-norepinephrine (0.0012 mg./kg. i.v.) sometimes evoked a pronounced increase in the diuresis lasting over two hours. If the blood pressure rise was great diuresis was decreased. Epinephrine

(0.002 mg./kg. i.v.) produced only a slight increase in the diuresis of short duration.

In human beings, Werko et al (1951), and Smythe et al (1952), found only a small influence on diuresis with the adrenal medullary hormones l-epinephrine and l-norepinephrine, usually an increase. The glomerular filtration rate was constant despite an increase in arterial pressure. A decrease in the excretion of sodium and potassium was attributed to an increase in tubular reabsorption by Smythe et al (1952). Jacobson, Hammarsten and Heller, (1952), confirmed, in general, the observations of Smythe et al. They found that the constant infusion of adrenaline at the rate of 10 to 18 ug./min. caused a decrease in renal plasma flow, a decrease in glomerular filtration rate, and an increase in filtration fraction. There was a decrease in the excretion of sodium, potassium and chloride. Others (Moyer and Handley, 1951; Churchill-Davidson, Wylie, and Miles, 1951; Pickford and Watt, 1951) found renal blood flow and glomerular filtration rate usually reduced with both l-epinephrine and l-norepinephrine. Duncan et al (1951), found 0.4 mg of adrenaline in oil every four hours in humans caused an increase in sodium and chloride, and a decrease in potassium excretion. No consistent change occurred during the administration of adrenaline in saline.

Salyrgan

Although the mercurials are widely used clinically,

their mechanism of action is still unclarified. At present, they are believed to act by inhibiting tubular reabsorption of water and electrolytes (Bantram, 1932; Schwartz and Wallace, 1951; Rice, Frieden, and Smith, 1953; Farah, Cobbey and Mook, 1952). Ionizable mercury appears to be the active constituent of these compounds, hence the superiority of the ionizable compounds (Sollman, Schreiber, and Cole, 1936). Most workers find little or no changes in the glomerular filtration rate or the renal plasma flow caused by these compounds (Brodsky and Granbarth, 1953; Schwitz, 1932; Walker et al (1937). Salyrgan, has been reported as having a pronounced effect on electrolyte excretion (Blumgart, Gill, and Levy, 1934; Berliner and Kennedy, 1948; Weston and Escher, 1948; Mudge, Ames and Foulks, 1950; Pitts and Duggan, 1950, Schwartz and Wallace, 1951; Citron, Bercu, Lemmer and Massie, 1951; Brodsky and Granbarth, 1953; Rice, Frieden and Smith, 1953). Sodium and chloride are freely excreted, while potassium is conserved, i.e. salyrgan does not interfere with the tubular reabsorption of potassium. Berliner and Kennedy, 1948; Mudge, Ames and Foulks, 1950; Schwartz and Wallace, (1951). Some workers found an increase in potassium excretion (Blumgart, Gill and Levy, 1934). Altschule (1953), found an increase in potassium excretion in sodium depleted individuals.

Evidence is accumulating (Rice et al, 1953) that chloride ion is the ion principally affected by the mercurials,

with sodium excretion following passively. With the inhibition of chloride and sodium reabsorption, these particles are osmotically active and produce the resulting diuresis. This hypothesis is supported clinically and experimentally by the finding that chloride depletion leads to refractoriness of the kidney with respect to the diuretic effect of the mercurials, while the administration of chloride salts leads to a recovery of their diuretic potency (Hilton, 1951). Further support for the hypothesis is presented by Rice et al (1953), in experiments in which they diminished the activity of a mercurial by substitution of sodium nitrate for sodium chloride in the vascular compartment of the dog.

Several attempts have been made to link the diuretic activity of mercurials to the inhibition of some particular enzyme system. These attempts were based on the assumption that ionizable mercury combined with one of the many enzymes so important in metabolism.

Handley and Lavik (1950), found inhibition of the succinic dehydrogenase system of the kidney by mercurial diuretics. The fact that the inhibition could be reversed by BAL supports the assumption that the mercurials act by combining with critical sulfhydryl groups. Fawaz (1951), found no influence on oxygen uptake of kidney slices or on the succinic oxidase activity when diuretic doses of mercurials were given. As pointed out by Fawaz, the fact that BAL reverses the action

of mercurials is no proof that mercurial diuretics act by inhibiting sulfhydryl containing enzymes. It only means that BAL binds mercury more firmly than the tissues.

Cohen (1953), attempted to show an inhibition of ATP production with mercurials, but found inhibition only with doses many times the diuretic dose.

Since the mercurials inhibit sodium and chloride reabsorption mechanisms (Citron et al, 1953; Schroeder, 1951), a high incidence of extracellular fluid sodium and chloride depletion results when the drug is coupled with salt restriction. This fact becomes important as the "low salt syndrome" may develop clinically.

Dextrose

The literature on the diuretic action of dextrose is extremely limited. The general view is that dextrose is an "osmotic" diuretic whenever it exceeds the kidney threshold and spills over into the urine. The dextrose produces diuresis by its osmotic activity which holds water in the kidney tubules for excretion instead of being reabsorbed.

In a study of the diuresis of diabetes mellitus, Brodsky, Rapoport and West (1950), concluded the diuresis to be dependent only on the number of osmotically active particles being excreted. In man, Tarail et al (1951), found dextrose to have no value as a diuretic. A 25% dextrose solution greatly increased the urine flow, but losses of water did not exceed

the volume of fluid administered. The excretion of potassium and chloride usually rose temporarily and then fell. The excretion of sodium was usually too small to produce appreciable reduction of increased stores of sodium.

Selkurt (1937), found hypertonic dextrose solution, in the dog, did not increase the glomerular filtration rate as measured by creatinine. Bonsnes and Band (1936), however, found an increase in the glomerular filtration rate of about 1.25 times the control values.

Sorbitol

Sorbitol is a hexahydric alcohol, produced by the reduction of dextrose. West et al, (1938), showed it to have 1.88 times the osmotic pressure as the same percentage sucrose solution. Sorbitol increased the urine output from the control value of 20 ml. per 15 minutes to 160 ml. per 15 minutes after the intravenous injection of 50 ml. of a 50% sorbitol in the dog. Burget et al, (1937), also working with the dog, reported repeated injection of 50% sorbitol solution over a period of several days gives no evidence of any toxic effects. Lindberg (1939), also showed sorbitol to be non-toxic to the dog kidney. Rapaport, Brodsky, West and Mackler (1949) have data supporting their hypothesis that urinary flow is simply dependent on the concentration of the loading solute in osmotic diuresis. Sorbitol was among the solutes studied.

Strohm (1938), used 50% sorbitol solution intravenously in dogs and found it equal to sucrose in its diuretic activity. Sorbitol was also used clinically in a patient who had almost complete anuria for several days and failed to respond to i.v. glucose, sucrose or sorbitol until the dose of sorbitol was increased to 1 cc./lb. Almost overnight 200 cc. of 50% sorbitol caused the output to equal the intake.

CHAPTER II

STATEMENT OF THE PROBLEM

This study is concerned with the investigation of four compounds: arterenol, salyrgan, dextrose, and sorbitol. Each is being studied for its effect on glomerular filtration rate (GFR), renal plasma flow (RPF), urine flow, and the excretion of sodium, chloride, and potassium.

Arterenol is being investigated because studies on l-norepinephrine alone have been sparse. Most of the work has been done on rats with only a few reports on the dog. A few studies have been done on human beings. Salyrgan, though widely studied clinically, deserves more attention with respect to its mechanism of action. Dextrose and sorbitol have received hardly any study as diuretics. The effect of dextrose on the glomerular filtration rate (creatinine clearance) has been studied incidentally, as part of other problems, but no study of electrolyte excretion has been made, while sorbitol has not been studied with respect to its mechanism of diuretic action.

CHAPTER III

METHODS

Male and female mongrel dogs were lightly anesthetized with nembutal or chloralose and hydrated with 0.5% NaCl (15 ml./kg. i.v.). The hypotonic NaCl solution was given through the right femoral vein. The left femoral vein was exposed and blood samples withdrawn at definite intervals. At the time of hydration, p-aminohippuric acid and creatinine were injected subcutaneously (50 and 100 mg/kg. respectively). The bladder was catheterized with a #9 plastic catheter, and the bladder emptied. The first collection period began about thirty minutes after the hydration.

The carotid artery was cannulated and the blood pressure was recorded by a mercury manometer. A direct writing electrocardiograph recorded any changes in the electrocardiogram.

The drugs under study, were given through the right femoral vein by injection either directly into the vein or into the rubber tubing attached to the cannula. The urine collection periods were each thirty minutes long. At the middle of each period, blood samples were taken from the left femoral vein and later analyzed for creatinine and p-aminohippuric acid. A similar analysis was made on the urine samples, and in addition,

the urine was analyzed for sodium, chloride, and potassium.

Creatinine was determined by the method of Folin (1919), and its renal clearance considered equivalent to the glomerular filtration rate (GFR). p-Aminohippuric acid was determined by the method of Smith et al. (1945), and its renal clearance considered equivalent to the renal plasma flow (RPF). Chloride was determined by iodometric titration using the method of Sendroy (1937). Sodium and potassium were determined by flame photometry (Perkin-Elmer Instruction Manual), Willard, Merritt, Dean.

CHAPTER IV

RESULTS AND DISCUSSION

Arterenol

Table 1 presents a comparison between the average control values, and the average values after the intravenous administration of arterenol (0.001 mg./kg.). The statistical analysis indicates no significant differences between the control period and the arterenol period.

TABLE I

THE EFFECT OF INTRAVENOUS ARTERENOL ADMINISTRATION ON URINE OUTPUT, GFR, RPF AND THE URINARY EXCRETION OF SODIUM, CHLORIDE AND POTASSIUM

PERIOD	URINE OUTPUT ML/30 min.	GFR (ml./min)	RPF (ml./min)	Reab.	UCl (mg./30 min.)	UNa (mg./30 min.)	UK (mg./30 min.)
control	25.8	61	151	0.972	78.7	71.2	49.1
arterenol	29.6	64	156	0.984	66.9	68.3	35.2
S^2 =	155.2	419.8	3932.8	4.07×10^{-4}	478.8	226	2856
$S_{\bar{x}}$ =	4.4	7.24	25.60	.0225	7.73	7.517	27.2
t =	0.862	0.414	0.1933	.533	1.525	0.385	0.511
P =	.5	.5	.5	.5	.2	.5	.5

S^2 = variance, $S_{\bar{x}}$ = standard error, t = ratio of difference between the means and $S_{\bar{x}}$, P = Probability

Explanation of symbols used in Table I

GFR, Creatinine Clearance--glomerular filtration rate in ml/min.
RPF, p-Aminohippuric acid clearance--renal plasma flow in ml/min.
Reab., Reabsorption of water by the tubules, Ml. reabsorbed per ml. of glomerular filtrate.
UCl, Urinary excretion of chloride, expressed in mg./30 minutes.
UNa, Urinary excretion of sodium, expressed in mg./30 minutes.
UK, Urinary excretion of potassium, expressed in mg./30 minutes.

Table I summarizes eight experiments, the original data of which appear in Table V.

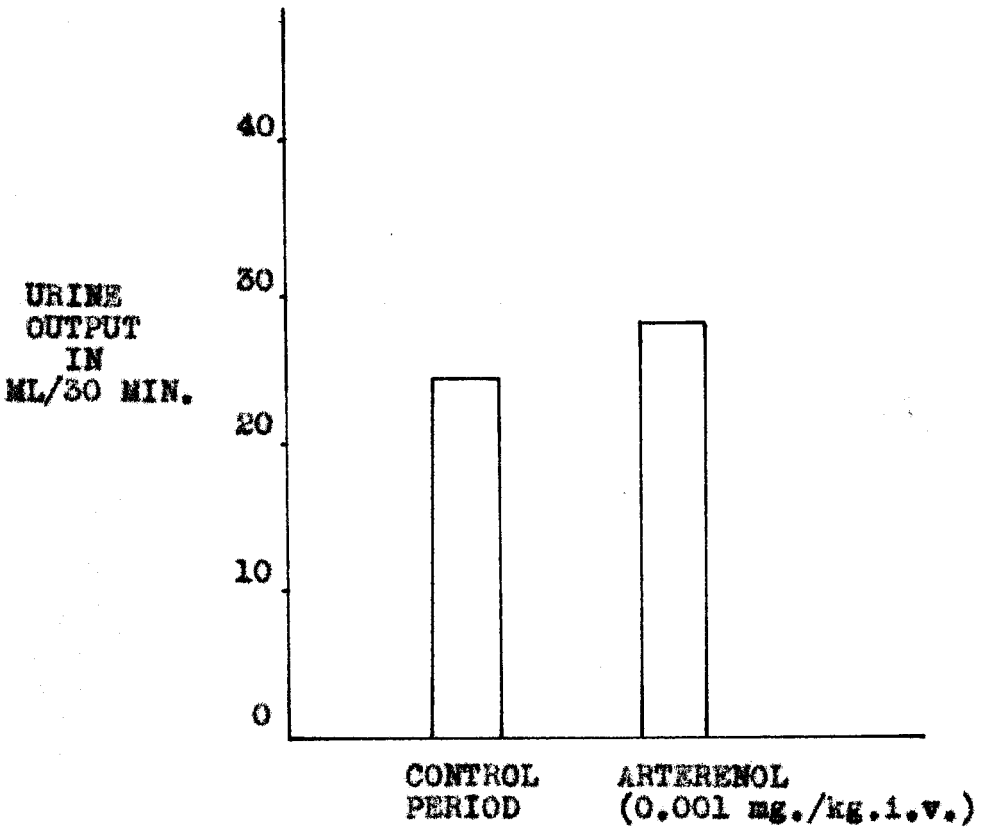
The blood pressure was not allowed to increase over 30 mm. Hg. It returned to preinjection levels in about two minutes. No changes were noted in the ECG.

Discussion

No consistent change occurred in these experiments. Results ranged from diuresis to antidiuresis. This was probably due, in part, to animal variation, however the evidence currently available indicates both of these effects can be obtained. The average values do not indicate any very significant changes except perhaps the decrease in potassium excretion. According to Dury (1951), epinephrine should be considered as having a role in potassium homeostasis. He found epinephrine (0.02 mg. per 100 gm. rat, s.c.) decreased the plasma potassium in normal rats. If such a result occurs in the dog, it is obvious that less potassium would be filtered, and therefore less excreted. Pullman and McClure (1952) found a decrease in the plasma potassium with l-norepinephrine in humans, indicating that we were

Fig. 1

COMPARISON BETWEEN THE CONTROL PERIOD AND THE PERIOD AFTER ARTERENOL WITH RESPECT TO URINE OUTPUT



probably getting the same effect in the dog. The small decreases in the excretion of sodium and chloride could be considered insignificant changes without need of explanation. We might, on the other hand, consider them significant changes which resulted from the increase in the reabsorption of water. As more water was reabsorbed by the tubules, more sodium and chloride was passively reabsorbed along with it. In man, Smythe et al (1952) was impressed with the idea of increased reabsorption for he says, "Urine flow usually increased somewhat during the action of the adrenal medullary hormones and fell off sharply on withdrawal, suggesting that these compounds interfere with the tubular reabsorption of water."

Although animal variation is undoubtedly a large factor in these results, various degrees of diuresis and antidiuresis can be elicited with this compound. This suggests that some variable in the administration is not being controlled. It may be that the rate of administration as well as the total amount are important in the result obtained. It should be noted that workers have previously reported inconstant results with respect to urine formation and even if they reported only diuresis or antidiuresis, such wide variation in response demands an explanation.

Schlegel (1953), suggest that the lack of agreement among various investigators as to the effect of epinephrine on water and electrolyte excretion may be due to differences in

the adrenergic activity of the adrenal medulla.

Leimdorfer (1953), found that if the blood pressure rise was too great, in the dog, antidiuresis resulted. With smaller rises in blood pressure there was an increase in the diuresis which was quite pronounced and which lasted over two hours.

On the basis of the reports in the literature and our own experiments we have to assume that the diuretic action is due to the rise in blood pressure and the subsequent increase of the GFR and by its action on the renal tubules which results in a decrease in the reabsorption of water and an increase in the excretion of chloride. Any increase in the excretion of chlorides has an additional osmotic action of its own, tending to retain water in the tubules.

Salyrgan

Table II presents a comparison between the average control values and the average values after the intravenous administration of salyrgan in amounts of 2 to 6 mg./kg. Statistical analysis indicates significant differences between the control and drug periods for the urine output, reabsorption and urinary excretion of sodium and chloride.

TABLE II

THE EFFECT OF INTRAVENOUS SALYRGAN ADMINISTRATION ON URINE OUTPUT, GFR, RPF, REABSORPTION, AND THE URINARY EXCRETION OF SODIUM, CHLORIDE AND POTASSIUM

PERIOD	$\frac{UV}{30}$ min.	GFR (ml./min.	RPF	Reab.	UCl (mg./30 min.)	UNa	UK
control	14.6	45	138	0.990	39.6	29.9	30.5
salyrgan	31.5	53	143	0.973	148.1	107.6	33.1
S^2 =	766.6	229.1	9120	1.612×10^{-5}	22070	1568.6	266.6
$S_{\bar{x}}$ =	6.714	3.907	36.1	4.015×10^{-3}	36.90	30.0	4.71
t =	2.517	2.05	0.138	4.23	2.94	2.586	0.552
P =	.05	.05	P 7.5	P .01	.02	.05	.5

For an interpretation of the symbols, see Table I.

Changes in the blood pressure were insignificant. Occasionally there was depression of the "T" wave of the ECG, or tachycardia.

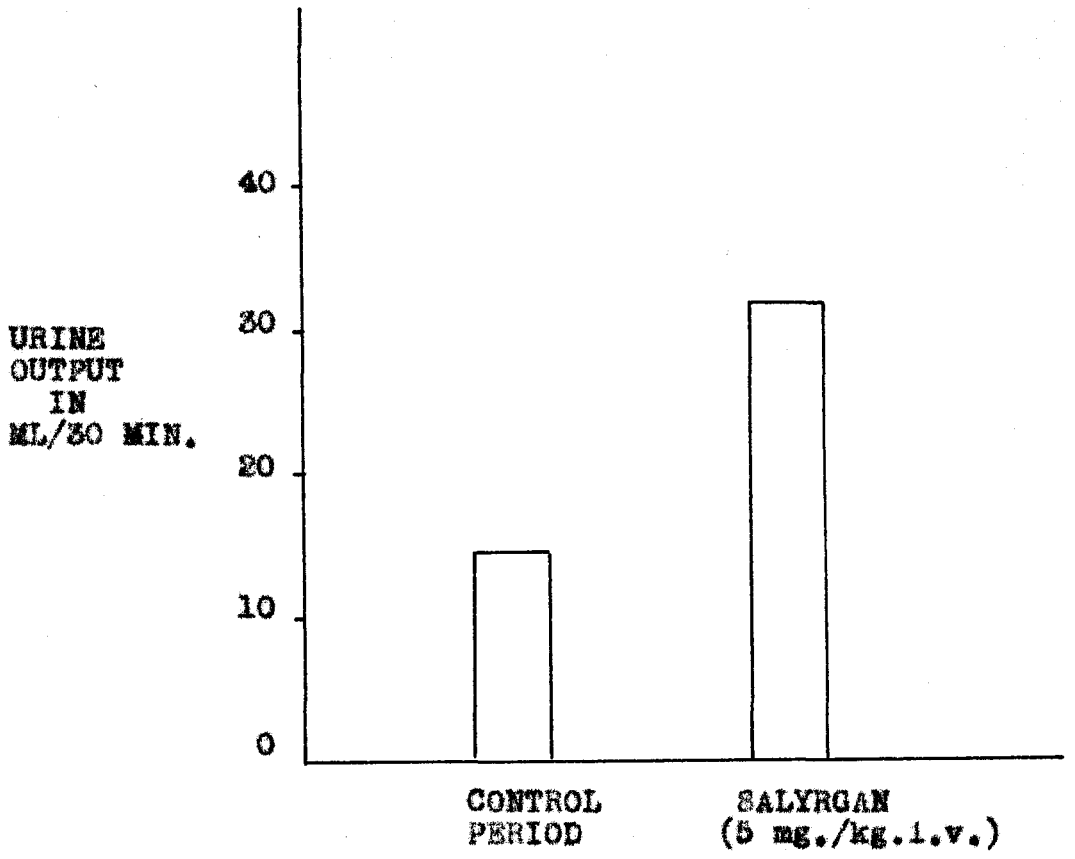
Figure 2 is a comparison between the control period, and the period after salyrgan with respect to urine output.

Salyrgan Discussion

The results of these experiments indicate that this diuretic acts by decreasing the reabsorption of water from the tubules and by increasing the excretion of sodium and chloride. GFR and RPF are essentially constant.

Fig. 2

COMPARISON BETWEEN THE CONTROL PERIOD AND THE PERIOD AFTER SALYRGAN WITH RESPECT TO URINE OUTPUT



Evidence is now accumulating which indicates that the principal and possibly only action of the mercurials is on the mechanism concerned with reabsorption of the chloride ion from the tubules (Rice et al., 1953). The results presented here support this hypothesis.

According to Rice et al. (1953), the inhibition of chloride reabsorption causes this ion and sodium ion to be excreted in the urine in increased amounts. Sodium ion follows chloride ion to maintain electrical neutrality. The excreted ions exert an osmotic action in the tubules which tends to hold water and cause it to be excreted in the urine.

It is interesting to note that potassium excretion increased only slightly while sodium and chloride increased a great deal. It appears that potassium reabsorption is unaffected by mercurials. This is in agreement with Berliner and Kennedy, 1948; Mudge, Ames and Foulks, 1950; Schwartz and Wallace, 1951; but contrary to Blumgart, Gill and Levy, 1934. Altschule (1953), found some patients excreted more potassium than sodium in sodium depleted individuals.

Some important dangers to Salyrgan's use deserve mention. Mercurial poisoning of the kidney and heart may result from prolonged use. Depletion of sodium, chloride and sometimes potassium may result especially when coupled with salt restriction. This derangement of the extracellular fluid produces the "low salt syndrome" clinically.

Dextrose

Table III presents a comparison between the average control values, and the average values after the intravenous administration of dextrose (2.0 ml./kg. 50% solution). Statistical analysis indicates significant differences between the control and drug periods for urine output, GFR, reabsorption, and urinary excretion of potassium.

TABLE III

THE EFFECT OF INTRAVENOUS DEXTROSE ADMINISTRATION ON URINE OUTPUT, GFR, RPF, REABSORPTION, AND THE URINARY EXCRETION OF SODIUM, CHLORIDE, AND POTASSIUM

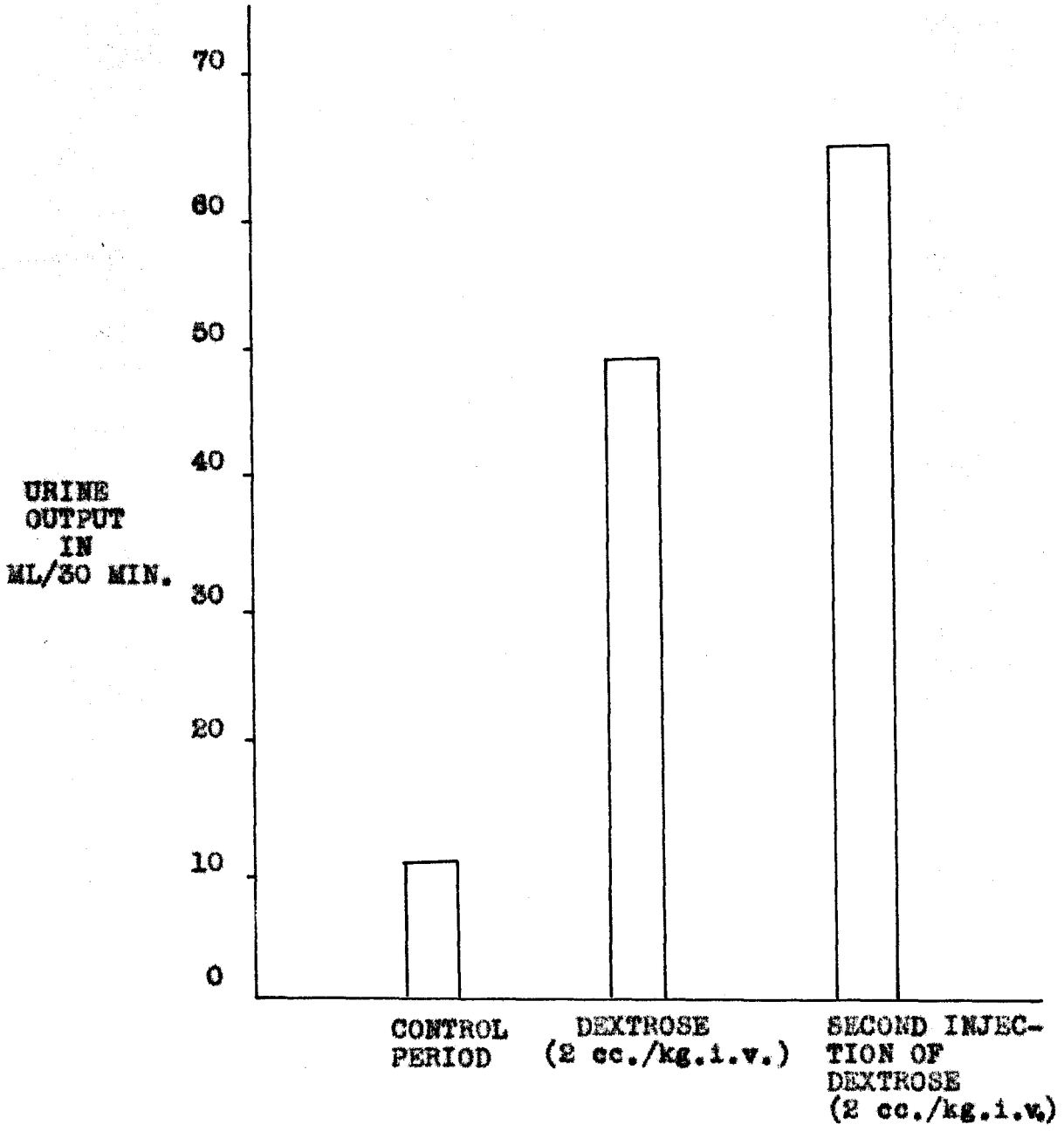
PERIOD	$\frac{UV}{30 \text{ min.}}$	$\frac{UV}{\text{min.}}$	GFR (ml/min.)	RPF	Reab.	UCl (mg./30 minutes.)	UNa	UK
control	10.3	0.34	62	240	0.994	31.1	16.6	29.4
dextrose	40.2	1.34	86	301	0.984	51.1	28.2	54.5
For an interpretation of the symbols, see Table I.								
S^2 =	114.1		245.5	4790	9.166×10^{-5}	527.8	100.8	193.7
$S_{\bar{x}}$ =	4.77		7.00	36.02	3.617×10^{-3}	8.684	4.49	6.224
t =	6.268		13.425	1.69	2.764	2.303	2.583	4.0327
P =	.01		.02	.01	.05	.05	.05	.02

In several experiments, a second injection (2 ml./kg., 50% soln.i.v.) was given. It was found that the urine output was again increased to 68.2 ml per minute on the average.

Table VII presents the original data for all the

Fig. 3

COMPARISON BETWEEN THE CONTROL PERIOD AND THE PERIOD AFTER DEXTROSE WITH RESPECT TO URINE OUTPUT.



dextrose experiments.

Figure 3 is a comparison between the control period and the period after dextrose injection with respect to urine output.

Discussion

The results of these experiments indicate that in every experiment except one there was an increase in the GFR and RPF. In one experiment, there was no change. A good diuresis was always obtained.

The increase in the GFR is in agreement with Bonsnes and Dana (1936), who also found a considerable increase. The explanation for this increase in GFR is probably found in the expansion of the blood volume which in turn brings about an increase in the GFR. The expansion of the blood volume is due to the hypertonic dextrose solution itself, and to its ability to attract water from the extracellular fluid further expanding the blood volume.

There is evidence that the kidney can regulate both the composition and volume of the extracellular fluid. It is probable that one mechanism for reducing the fluid load is by increasing the GFR. The available evidence indicates that the GFR does vary under certain experimental conditions, though not usually.

Ladd and Raisz (1949), showed that isotonic sodium chloride given intravenously, or added to the diet in amounts up to four grams per kilograms, induced changes in the GFR of

up to 100% over control values.

Evidence is also available that in certain conditions there is a marked decrease in the GFR. According to Merrill (1946), the GFR is reduced to 1/2 to 1/3 of the normal value in patients with congestive heart failure.

Shannon (1936), has shown that the GFR tends to increase with increasing urine flow and diminish with low urine flows, but his general conclusion is that there is too small a change to be considered a mechanism by which the kidney regulates the volume of the body fluids. Shannon simply varied the water intake of his animals, however, to produce the variation in urine flow.

My own suggestion is that a large extracellular fluid load which is isotonic or hypertonic can increase the GFR. According to our present conception, the antidiuretic hormone is liberated whenever the extracellular fluid becomes hypertonic. In this situation, the kidney must overcome the activity of the antidiuretic hormone and increase the GFR in order to dispose of a large fluid load. This is probably accomplished by a small increase in the blood pressure and by dilatation of the vascular system of the kidney. The increase in the RPF supports this assumption.

If it is true that as the hypertonic fluid load increases the GFR also increase, two mechanisms would be operating to produce the diuresis: the increase of the glomerular filtra-

tion rate, and the osmotic action of the unabsorbed substances in the tubules. This osmotic action tends to hold water in the tubules so that it becomes part of the urine.

The increase in the electrolyte excretion (sodium, chloride, potassium), is explained by the increased glomerular filtration rate and the "washing out" effect which is produced by the greater urine flow. There is less time for the active reabsorptive mechanisms to operate and reclaim the increased amount of electrolyte presented to the tubules.

Since the excretion of electrolytes is increased, there is danger of salt depletion, especially when coupled with salt restriction.

Sorbitol

Table IV presents a comparison between the average control values and the average values after the intravenous administration of sorbitol in amounts of 2.5 ml./kg. of a 50% solution. Statistical analysis indicates significant differences between the control and drug periods for urine output and RPF.

TABLE IV

THE EFFECT OF INTRAVENOUS SORBITOL ADMINISTRATION ON URINE OUTPUT, GFR, RPF, REABSORPTION AND THE URINARY EXCRETION OF SODIUM, CHLORIDE, AND POTASSIUM

PERIOD	$\frac{UV}{30 \text{ min.}}$	$\frac{UV}{min.}$	GFR (ml./min.)	RPF	Reab.	UCl (mg./30 minutes)	UNa	UK
control	15.3	0.51	60	72	0.983	64.5	32.0	49.8
sorbitol	74.4	2.48	71	184	0.959	112.5	77.6	38.8
s^2 =	1088		648.4	1021	2.211×10^{-4}	8891	4432	2021.8
$s_{\bar{x}}$ =	12.47		10.4	18.45	0.01777	55.64	25.16	18.35
t =	4.739		2.211	7.86	1.350	1.3468	1.8124	.59945
P =	.01		.05	.02	.2	.2	.1	.5

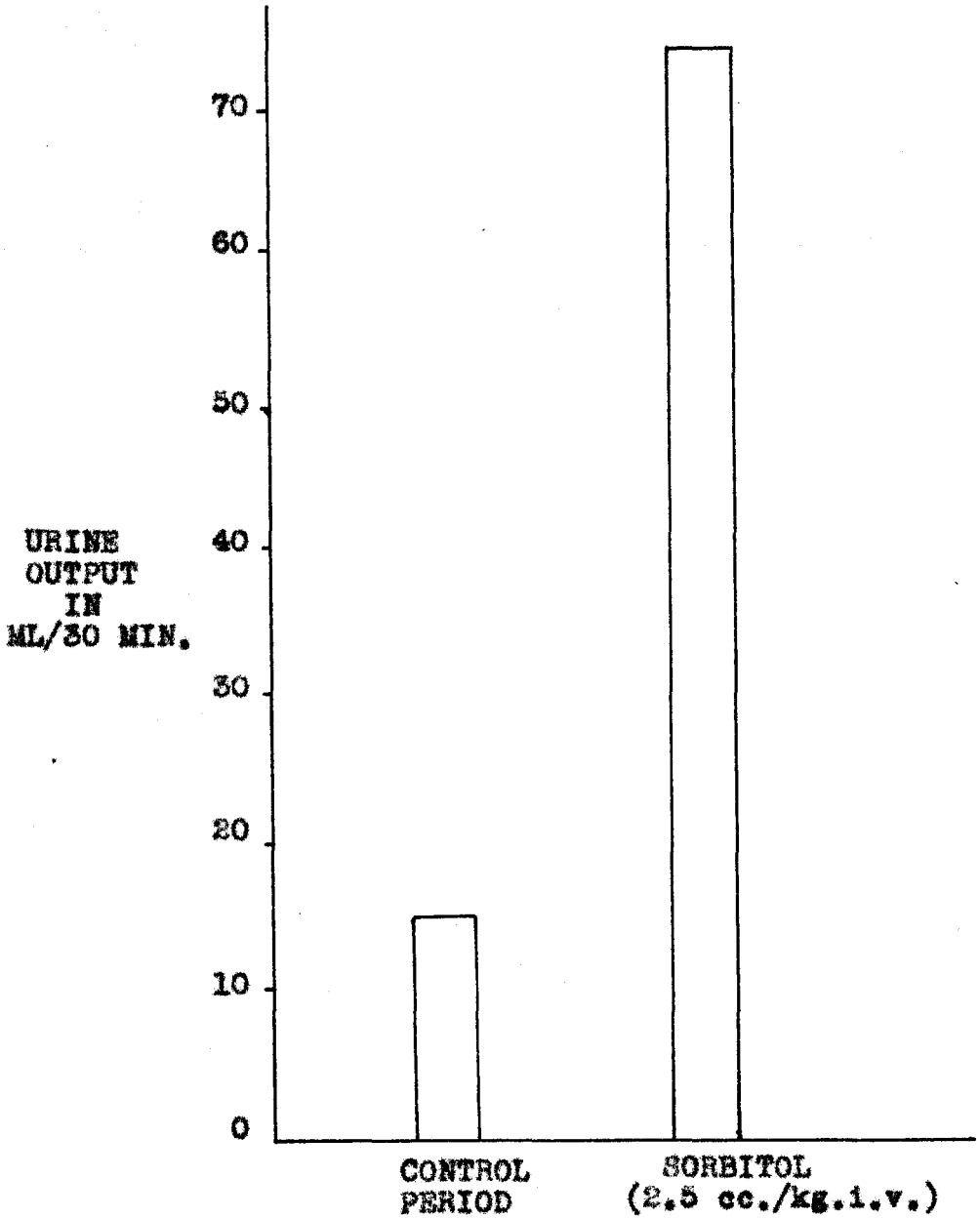
For an interpretation of the symbols, see Table I.

In several experiments, a second injection of sorbitol was made, which resulted in a further increase in the urine output (to 4.8 ml./min.) and electrolyte excretion.

As in the case of dextrose several mechanisms appear to be operative. There is an increase in the GFR and RPF. This increase is similar to the increase after dextrose injection and probably arises for the same reasons. The urine output is considerably larger after sorbitol however. The hypertonic sorbitol solution draws water from the interstitial fluid to further expand the vascular compartment after the initial load of 2.5 ml/kg. of 50% sorbitol solution. There is a small increase in the

Fig. 4

COMPARISON BETWEEN THE CONTROL PERIOD AND THE PERIOD AFTER SORBITOL WITH RESPECT TO URINE OUTPUT



blood pressure. Dextrose, sorbitol, and probably any compound in sufficient concentration to increase the tonicity of the plasma, appears to increase the GFR and RPF. It is assumed this is due to expansion of the extracellular fluid volume, and the increase in the blood pressure. Under the circumstances of a large hypertonic fluid load, the kidney is teleologically required to excrete the load in spite of the fact that the kidney is handicapped due to the liberation of the anti-diuretic hormone. The kidney overcomes this handicap by increasing the GFR.

According to Chamber, Mevlille, Hare, and Hare (1945), it is the change in the osmotic pressure of the plasma rather than changes in any specific ingredient (sodium, chloride, etc.) that determines the response of the neurohypophysis in releasing antidiuretic hormone. With the administration of sorbitol, the osmotic pressure of the plasma is increased.

The decrease in reabsorption is due to the action of the unabsorbed substances in the tubules. These substances retain water in the tubules by their osmotic action and this water is excreted as urine.

There is an increase in the electrolyte output of chloride, sodium, and potassium. This increase is again due to an increase in the GFR, and as more fluid is presented to the tubules per unit of time, less is reabsorbed by the tubules. The greater electrolyte load in the tubules also adds to the osmotic action which reduces the reabsorption of water.

Sorbitol, as a diuretic, has the advantage of being non-toxic to the kidney, producing a profuse diuresis and remaining in the vascular compartment longer than dextrose, since it is metabolized more slowly. As in the case of dextrose and salyrgan, there is danger of depletion of sodium and chloride. Potassium excretion is probably not greatly changed, even though our experiments indicated a small decrease. According to the results of these experiments, arterenol is both diuretic and anti-diuretic. The other drugs studied are distinctly diuretic.

CHAPTER V

SUMMARY

Arterenol

1. On the basis of our experiments and conforming with the reports about the diuretic action of arterenol (Eversole; Drill and Bristol; Leimdorfer) we have to assume that generally arterenol produces an increase in the urine output.

2. The increase in the urine output may be explained by the rise in blood pressure and the subsequent increase in the GFR and by its action on the renal tubules (decrease of the reabsorption of water and increase of the chloride excretion).

Salyrgan

1. The diuretic action of salyrgan is not due to an increase in either the GFR or RPF, these functions do not change.

2. The principal action of salyrgan in producing diuresis is the decrease in the reabsorption of water from the tubules.

3. The decrease in reabsorption is probably brought about by the osmotic action of the electrolytes, which are excreted in increased amounts.

4. The mechanism for the reabsorption of chloride

is inhibited by the mercurials leading to a pronounced increase in the excretion of chloride. Sodium, and under certain conditions, potassium excretion follows chloride excretion passively in order to maintain electrical neutrality.

Dextrose

1. Dextrose exerts a diuretic effect by increasing the GFR, RPF and the excretion of chloride, sodium, and potassium. In addition dextrose exerts an osmotic action in the tubules which together with the electrolytes and other solutes retards the reabsorption of water.

2. The increase in the GFR and RPF is assumed to be due to the increase in the blood volume, and a small increase in blood pressure.

Sorbitol

1. Sorbitol increases the osmotic pressure of the blood more than an equivalent amount of sucrose.

2. The GFR and RPF increases. This is assumed to be due to the increase in the blood volume together with a small increase in blood pressure.

3. Sorbitol plus the other electrolytes and solutes of the plasma exert an osmotic pressure in the tubules and retard the reabsorption of water.

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ARTERENOL EXPERIMENTS *

TABLE V

Date	Wt. Kg.	PER	UV / 30 min.	UV / min.	GFR (ml./min)	RPF	Reab.	UCl (mg./30 minutes)	UNa	UK	B.P. mm.Hg.
4/15	19.0	(c)	25.9	0.74	78	--	0.990	37.7	--	--	145
		(d)	18.5	0.62	77	--	0.992	22.3	--	--	150
5/7	10.0	(c)	19.0	0.63	62	238	0.990	72.5	95.0	132	155
		(d)	52.0	1.71	51	172	0.966	40.6	97.0	49	180
5/21	11.8	(c)	38.2	1.09	58	148	0.981	140	--	--	110
		(d)	38.5	0.96	54	156	0.982	116	--	--	150
6/5		(c)	42.0	1.40	87	160	0.983	21.9	--	--	--
		(d)	45.0	1.50	71	165	0.978	28.8	--	--	--
6/9	11.0	(c)	21.4	0.71	49	110	0.985	89.5	--	--	135
		(d)	16.3	0.54	30	48	0.982	68.8	--	--	165
7/6	9.0	(c)	40.5	1.35	88	--	0.853	165	122	33.0	135
		(d)	42.0	1.40	123	--	0.989	136	99	9.5	155
7/13	21.4	(c)	15.6	0.52	44	210	0.988	93	65	17	170
		(d)	20.0	0.66	52	260	0.989	117	74	60	200
10/25	8.4	(c)	4.0	0.13	26	42	0.995	9.8	3.3	14.6	--
		(d)	4.5	0.15	57	137	0.997	7.0	3.7	22.3	--

Explanation of Symbols Used in Table V-VIII

UV, Urine Volume--ml/30 minutes and ml./minute.
GFR, Creatinine Clearance--glomerular filtration rate expressed in ml./min.
RP F, p-Aminohippuric acid clearance--renal plasma flow expressed in ml./min.
Reab., Reabsorption of water by the tubules, ml. reabsorbed per ml. of glomerular filtrate.
UCl, Urinary excretion of chloride, expressed in mg./30 minutes.
UNa, Urinary excretion of sodium, expressed in mg./30 minutes.
UK, Urinary excretion of potassium, expressed in mg./30 minutes.
PER., Period of urine collection--(c), is equivalent to control period, (d), is equivalent to drug period (arterenol).
B.P., Blood pressure in mm. Hg.
Wt., Weight of animal in kilograms.

* Comparison between the control period and the period after the intravenous injection of arterenol (0.001 mg./kg. i.v.).

SALYRGAN EXPERIMENTS

TABLE VI

Date	Wt. Kg.	Per.	$\frac{UV}{30 \text{ min.}}$	$\frac{UV}{\text{min.}}$	GFR (ml./min.)	RPF	Reab.	UCl (mg./30 minutes)	UNa	UK	B.P. mm.Hg.
4/28	9.0	(c)	8.7	0.29	40	--	0.993	26.6	--	--	140
		(5)	32.8	0.94	45	--	0.979	110.0	--	--	135
4/30	12.0	(c)	27.0	0.90	25	--	0.964	90.0	--	--	145
		(5)	20.0	0.57	47	--	0.988	71.0	--	--	135
7/16	14.0	(c)	24.5	0.82	63	140	0.987	79.0	72.5	48.0	120
		(6)	48.0	1.54	68	164	0.977	140.0	130	35.6	115
7/21	18.9	(c)	29.0	0.97	99	451	0.993	115	106	45.3	135
		(5)	32.5	1.08	81	270	0.987	122	131	39.3	140
7/28	6.0	(c)	22.0	0.73	28	--	0.974	62	--	--	135
		(6)	37.8	1.26	11	--	0.881	214	--	--	100
7/30	13.0	(c)	5.7	0.19	19	44	0.990	3.1	10.6	9.1	--
		(3)	7.0	0.26	54	126	0.998	6.5	17.8	12.0	--
9/1	13.1	(c)	12.0	0.40	50	--	0.992	19.9	4.3	28.1	150
		(6)	13.8	0.47	76	--	0.994	16.1	3.7	13.7	150
9/8	13.4	(c)	8.4	0.28	53	--	0.997	58.1	31.9	48.0	155
		(6)	12.0	0.40	50	--	0.993	54.5	52.7	59.0	150
9/14	12.2	(c)	7.5	0.25	70	--	0.996	24.0	19.3	--	165
		(6)	12.0	0.40	63	--	0.993	49.6	33.1	--	175
9/16	12.7	(c)	6.5	0.22	47	--	0.995	8.3	--	--	--
		(6)	11.5	0.38	67	--	0.994	28.3	--	--	--

TABLE VI (Cont.)

Date	Wt. Kg.	Per.	$\frac{Uv}{30}$ min.	$\frac{UV}{min.}$	GFR (ml./min.)	RPF	Reab.	UCl (mg./30 minutes)	UNa	UK	B.P. mm.Hg.
9/22	12.5	(c)	15.0	0.50	--	--	--	43.2	43.4	42.3	--
		(2)	17.1	0.57	--	--	--	51.8	26.7	32.4	--
9/23	11.3	(c)	4.5	0.15	--	--	--	6.5	16.8	12.2	--
		(6)	14.6	0.49	--	--	--	70.2	53.1	12.3	--
10/7	14.0	(c)	16.5	0.55	34	91	0.984	29.5	26.2	49.8	--
		(6)	18.0	0.60	24	35	0.974	54.5	45.9	37.5	--
10/14	11.8	(c)	6.5	0.22	33	81	0.998	31.7	13.3	37.4	--
		(6)	37.5	1.25	49	157	0.974	226	153	35.8	--
10/16	9.5	(c)	8.5	0.28	52	--	0.994	39.2	9.4	14.0	--
		(6)	110.0	3.66	73	--	0.953	597	356	60.0	--
10/19	11.8	(c)	4.0	0.13	36	97	0.996	13.1	16.6	17.9	--
		(6)	32.7	1.07	47	173	0.977	256	142	24.1	--
10/21	10.0	(c)	11.0	0.37	32	62	0.989	24.2	18.4	13.4	--
		(6)	77.0	2.57	38	73	0.932	450	253	35.8	--

For an interpretation of the symbols, see Table V.
(c), represents the control period
The number in brackets represents the amount of salyrgan in milograms.

DEXTROSE EXPERIMENTS

TABLE VII

Date	Wt. Kg.	Per	$\frac{UV}{30}$ min.	$\frac{UV}{min.}$	GFR (ml./min.)	RPF (ml./min.)	Reab.	UCl (mg./30 minutes)	UNa (mg./30 minutes)	UK (mg./30 minutes)	B.P. mm.Hg.
5/13	18.0	(c)	10.0	0.29	51	370	0.994	0.9	2.3	47.5	130
		(d)	46.0	1.54	82	408	0.981	4.8	12.4	82.0	135
6/2	10.9	(c)	4.1	0.14	25	52	0.995	4.5	--	--	120
		(d)	19.0	0.63	52	94	0.988	23.6	--	--	100
6/24	7.5	(c)	5.6	0.19	44	--	0.996	9.9	13.7	42.3	140
		(d)	23.5	0.79	95	--	0.992	34.0	41.8	44.9	140
8/11	12.8	(c)	6.5	0.22	95	198	0.998	12.3	55.4	24.4	145
		(d)	52.0	1.73	113	--	0.985	80.7	65.6	60.0	160
		(d)	71.5	2.38	158	200	0.985	56.5	73.5	38.2	145
8/13	14.5	(c)	7.1	0.24	98	341	0.998	5.8	4.2	21.1	160
		(d)	43.0	1.43	97	502	0.985	17.1	4.8	39.1	180
		(d)	70.0	2.33	45	173	0.949	27.0	3.2	32.1	170
8/27	17.6	(c)	6.0	0.20	69	--	0.997	11.1	7.54	11.6	140
		(d)	36.0	1.20	89	--	0.987	25.4	16.6	41.3	150
		(d)	63.0	2.1	69	--	0.967	40.2	25.5	37.2	150
4/24	15.0	(c)	32.5	1.08	56	--	0.981	173.0	--	--	110
		(d)	62.0	2.06	75	--	0.972	172.0	--	--	110

For an interpretation of the symbols, see Table V.

(d), dextrose solution, 2 ml./kg. 50% solution.

SORBITOL EXPERIMENTS

TABLE VIII

Date	Wt. Kg.	Per.	UV/30 min.	UV/min.	GFR (ml./min.)	RPF (ml./min.)	Reab.	UCl (mg./30 minutes)	UNa (mg./30 minutes)	UK (mg./30 minutes)	B.P. mm.Hg.
6/19	13.6	(c)	25.1	0.34	--	--	0.987	136.5	85.0	36.6	145
		(d)	74.1	2.47	92	--	0.973	110.9	93.0	36.8	165
6/12	13.6	(c)	15.4	0.51	40	55	0.987	33.4	17	87.3	150
		(d)	33.0	1.10	95	225	0.985	24.4	39.9	8.4	170
6/29	11.3	(c)	19.3	0.65	46	--	0.986	57.9	32.1	43.1	145
		(d)	54.0	1.80	67	--	0.973	37.3	27.8	15.8	110
7/1	13.0	(c)	15.3	0.51	85	--	0.994	123.5	--	--	155
		(d)	76.0	2.53	68.0	--	0.963	136.1	--	--	165
7/10	8.4	(c)	7.5	0.25	6	--	0.959	15.0	5.8	5.9	150
		(d)	55.0	1.83	23	78	0.922	96.6	38.0	18.8	140
7/24	16.5	(c)	18.0	0.60	23	84	0.974	76.5	43.7	65.5	150
		(d)	109.0	3.60	69	240	0.948	131.0	77.8	68.5	170
		(c)	147.0	4.90	--	--	--	182.0	122.4	75.7	--
8/6	12.7	(c)	6.5	0.23	68.0	84	0.996	8.9	8.6	60.6	150
		(d)	120.0	4.0	84	193	0.952	251.	189.0	84.5	--
		(d)	140.0	4.7	--	--	--	357.0	192	57.3	--

For an interpretation of the symbols, see Table V.
(d), represents the intravenous administration of the drug, 2.5 ml/kg. 50%.
In these experiments the control period (c) is compared with the drug period (d).

APPROVAL SHEET

The thesis submitted by James W. Flesher has been read an 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.

May 18, 1954
Date

Alfred Leimdorfer, M.D.
Signature of Adviser