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Research Article

THE CAUSE OF DEATH IN EXPERIMENTAL ANURIA [1, 2]

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Winternitz and his associates (1) observed electrocardiographic changes in dogs rendered anuric by bilateral occlusion of renal arteries. These changes were so similar to those which had been previously reported by the present authors in experimental potassium poisoning (2, 3) that a common origin was suspected. A systematic experimental study of the association between anuria and potassium poisoning was therefore undertaken and forms the subject of the present report.

REVIEW OF LITERATURE

In 1822 Gaspard (4) and Ségalas (5) observed sudden death following the intravenous injection of urine; Voit (6) in 1868 first suggested that potassium might be the poisonous element. Astaschewsky (7) and Feltz and Ritter (8), followed a few years later by Beck (9) and Herringham (10), clearly demonstrated that the toxicity of urine samples varied with their potassium content, although certain other investigators continued to emphasize the importance of other toxic substances in urine (11 to 16). Both Beck and Herringham carefully pointed out that their experiments proved only that urine is toxic, not that potassium is responsible for the symptoms or for the fatal outcome of "uremia."

The suggestion that potassium might accumulate within the body and might be responsible for various "toxic" manifestations of renal disease is not new. Accurate determination of potassium concentration in serum was, however, necessary to establish this hypothesis, and technically reliable methods were unavailable until recently. All older estimations, and many of those published as recently as fifteen or twenty years ago (8, 17, 18), must therefore be accepted with reservations. More recent studies indicate that, although potassium is not regularly increased in the serum of patients with renal disease, even in the presence of severe azotemia (19) and in "uremia," sporadic elevations may be found (19 to 25). On the other hand, increase in the concentration of potassium in serum has been observed with some regularity in experimental animals with ligated ureters (21, 26, 27, 28) and with bilateral renal infarction (1).

Rationale of present experiments

There is nothing to indicate that the irregular increases in potassium of serum in anuria mentioned above were of sufficient magnitude to cause death, or even to produce lesser evidences of toxicity. Electrocardiographic changes only have been reported (1, 28), without other signs of cardiovascular insufficiency. Substances other than potassium, many of them fatally toxic when injected individually in large quantities, also accumulate during anuria (23). In the absence of any evidence other than its mere presence in serum in increased concentration, it is quite arbitrary to select one or another particular substance and assign to it a primary rôle in causing death.

To know if potassium is responsible for the death of anuric animals, it is essential to follow the electrocardiogram and the serum potassium concentration until the actual moment of death. The course may then be compared with that following intravenous injection of potassium salts in otherwise normal animals (2). A reasonable basis for the conclusion that potassium itself is the cause of death would be provided if the anuric animals should: (*1*) develop the same sequence of electrocardiographic changes with rising serum potassium as do normal animals (Figure 1); (*2*) survive until a concentration of serum potassium is attained at which normal animals die; (*3*) invariably die when such a concentration is reached; and (*4*) develop the same terminal electrocardiographic changes and die in the same way as do the controls. This conclusion would be strengthened if death occurred at the same concentration of serum potassium in ordinary anuric dogs and in those receiving added potassium, since the two groups would have in common only the single factor of the serum potassium concentration. Conversely, if these conditions should not be ful-

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[2] Preliminary report presented before the American Physiological Society, April 1941 (Am. J. Physiol., 1941, **133**, 331).

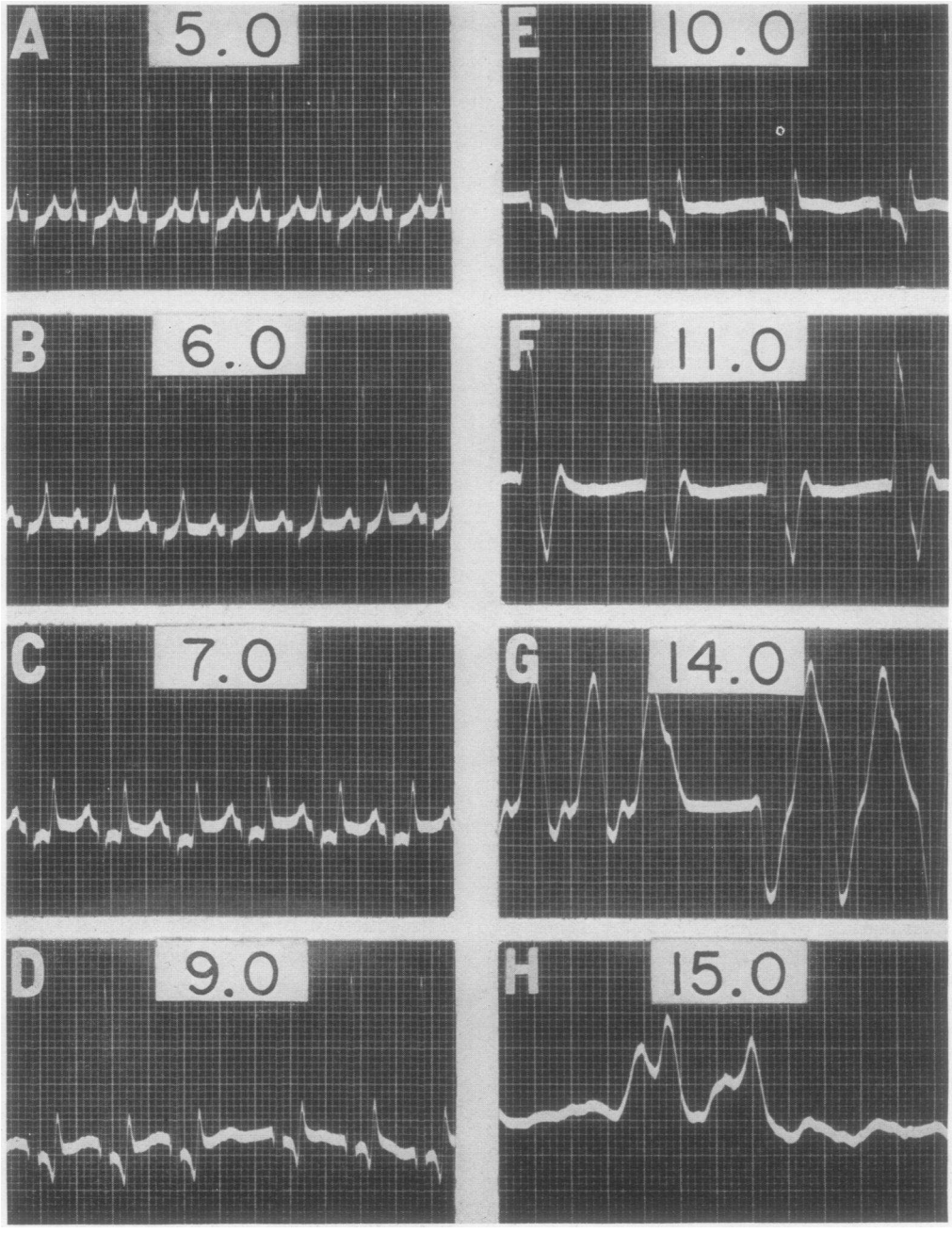

FIG. 1. NORMAL ANIMAL RECEIVING ISOTONIC KCl INTRAVENOUSLY AT A UNIFORM RATE UNTIL DEATH

The figures on each electrocardiogram indicate the usual concentrations of serum potassium associated with the changes it shows.

(A) Control, Lead II.
(B) T waves higher, beginning drop of S–T segment.
(C) Further increase in height of T waves and depression of S–T segment. The P waves are still intact.
(D) Disappearance of P waves. T waves diphasic.
(E) P waves remain absent, T waves diphasic. Beginning widening of QRS complexes.
(F) Marked QRS widening (intraventricular block).
(G), (H) Terminal disorganization of the entire complex.

filled, potassium accumulation is probably not the cause of death in anuria.

Since the validity of this method of attack rests in part on the specificity of the sequence of electrocardiographic changes induced by potassium, they will be described briefly. They are in the sequence in which they appear: (*1*) progressive heightening of the T wave, which often becomes diphasic, together with a drop in S–T segment, (*2*) disappearance of the P wave, (*3*) widening of the QRS complex, indicating intraventricular block, and (*4*) cardiac arrest.

This sequence is shown in Figure 1, together with the concentration of serum potassium associated with each change. Certain other changes, such as P–R dissociation, sometimes occur. The T wave is characteristically sharp in outline.

Although no individual change is pathognomonic of potassium effect, the sequence is so invariable and so uniquely characteristic when taken in its entirety that it is practically diagnostic of potassium poisoning.

METHODS AND MATERIALS

Three groups of dogs were employed. In the first the ureters were tied, in the second the kidneys were removed, while in the third a solution of mercuric chloride was injected intravenously. Operations were performed with full aseptic precautions under anesthesia induced by intraperitoneal nembutal or sodium amytal. Three to four mgm. of mercuric chloride per kilo of body weight were injected slowly into the femoral vein as a 0.1 per cent solution in isotonic saline. All animals given mercury became completely anuric within twelve hours, and in only one did urine flow later recommence, with eventual recovery. In the majority of the experiments food and water were withheld after anuria became established, since free drinking of water resulted in persistent vomiting and secondary chloride depletion. Animals showing dryness of mucous membranes or other evidences of dehydration received intraperitoneal injections of 500 or 1000 cc. of normal saline.

Electrocardiograms were taken from Lead II in all instances, using a Sanborn "Cardiette." Whole blood was usually employed for chemical determination of nonprotein nitrogen. Serum separated from blood allowed to clot under oil was employed for potassium, chloride and calcium analyses. Samples were taken from the femoral vein or, if the animal was moribund, directly from the heart. Nonprotein nitrogen was determined by a micro Kjeldahl technique (*29*); potassium as chloroplatinate by Hald's modification of the method of Shohl and Bennett (*30*); calcium by permanganate titration of an oxalate precipitate (*31*); and chloride by the method of Van Slyke (*29*). Before operation and at frequent intervals thereafter electrocardiograms and blood samples were taken. An attempt was made to be present at the actual moment of death, in order to obtain the terminal electrocardiogram and blood sample. This was successfully accomplished in about half of the experiments.

Certain observations on patients with advanced renal disease have been included for comparative purposes. All techniques were identical with those employed in experimental animals.

RESULTS

(*A*) *Experiments with anuria due to nephrectomy and to ureteral ligation*

The uncomplicated course of events following bilateral ureteral ligation was studied in twelve dogs; that following bilateral nephrectomy in six others. These two separate modes of producing anuria were employed because their pathological results differ (1, 32). Tables I and II, respectively, summarize these groups of experiments. The results in both groups are evidently very similar. Those of a chemical nature are: (*1*) progressive increase of serum potassium and of blood nonprotein nitrogen throughout the course of each experiment; (*2*) irregular decrease of serum chloride concentration; and (*3*) little change in calcium concentration. The electrocardiographic findings are: (*1*) changes in the T wave demonstrable within twenty-four to forty-eight hours, first appearing at potassium concentrations of 6 to 7 mM. per liter, and persisting in progressively intensified form throughout the course; (*2*) disappearance of P waves, usually after seventy to 100 hours, with serum potassium concentration of 9 to 11 mM. per liter; and, finally, (*3*) progressive widening of QRS complexes, followed within a few minutes, or at most within a few hours, by cardiac arrest and death. The widening of the QRS complex occurred only after the P wave had disappeared, and was associated with concentrations of serum potassium ranging from 12 to 20 mM. per liter. These electrocardiographic changes are illustrated in Figure 2, taken from a typical experiment following nephrectomy, and in Figure 3, taken from one with ureteral ligation. The changes are virtually indistinguishable from those in Figure 1 produced in normal animals by the intravenous injection of potassium. Furthermore, the concentrations of

potassium associated with each of these various changes are approximately the same as those observed in the animals with experimental potassium poisoning (2, 3).

No correlation could be found between the deficits of chloride sometimes observed (Table I, Experiments 1, 2, 3, 4, 8, and 13) and electrocardiographic changes. The large deficits in the first three experiments were due to the free administration of water by mouth, which induced severe vomiting. In the remainder of the experiments water was withheld and occasional injections of normal saline were given intraperitoneally, thus largely preventing chloride deficits. Since serum calcium was but little affected, it may be excluded as a disturbing factor.

Potassium chloride solutions in varying amounts were injected intraperitoneally into four dogs with ligated ureters and into five nephrectomized dogs immediately following the establishment of anuria. The results are summarized in Table III. The electrocardiographic sequence in a typical experiment is presented in Figure 4. This sequence is indistinguishable in character and progress from that of a normal animal receiving potassium continuously (Figure 1), and from that in anuric dogs without intraperitoneal injection of potassium (Figures 2, 3). The chemical changes are also qualitatively similar to those in anuric dogs receiving no potassium.

There are, however, significant quantitative differences between the group with uncomplicated anuria and the group receiving potassium. In Figure 5 are plotted the concentrations of potassium in serum at death in normal animals poisoned with potassium, in those with uncomplicated

TABLE I

Ureters ligated. Experiments in which no potassium was determined

Number	Time after ligation	Death	Blood NPN	Serum			Electrocardiographic findings			Remarks
				K	Cl	Ca	T wave changes	P waves disappear	QRS widening	
	hours		*mgm. per 100 cc.*	*mM. per liter*	*mM. per liter*	*mgm. per 100 cc.*				
1	0		41	6.0	108.6		0	0	0	Water given. Much vomiting. Saline given once.
	44		174	8.0	81.6		+	0	0	
	72		216	10.0	78.2		+	+	0	Death not observed.
	72–84	+								
2	0		29	5.9		9.1	0	0	0	Water given. Vomiting.
	24						+	0	0	Infusion.
	49		174	6.4	87.6	9.0	+	0	0	
	71						+	+	±	Death not observed.
	77–78	+		19.9						(Blood obtained after
	78		259	19.9	47.0	9.9				death.)
3	0		29	6.6	105.8	11.0	0	0	0	
	36		95	8.3	97.2		+	0	0	Water given. Vomiting.
	48		124	9.8	94.8		+	0	0	
	74			10.6	87.6	10.8	+	0	0	
	92		177	8.8	86.0		+	+	0	Infusion.
	107		194	9.9	89.6	10.2	+	+	0	
	115						+	0	0	
	125			10.5	89.2	10.7	+	+	±	
	128		221	11.2	90.4	9.8	+	±	±	
	132–139	+								Death not observed.
4	0		34	6.3			0	0	0	
	49						+	0	0	
	72		222	9.9	89.6		+	+	0	
	79–87	+								Death not observed.
5	0		25	5.9	109.4	11.3	0	0	0	
	53						+	0	0	One convulsion.
	70		169	9.7	109.4	10.4	+	0	0	
	122						+	+	0	
	142	+	341	14.5	104.6		+	+	+	Gradual decline to death.

TABLE I—*Continued*

Number	Time after ligation	Death	Blood NPN	Serum			Electrocardiographic findings			Remarks
				K	Cl	Ca	T wave changes	P waves disappear	QRS widening	
	hours		*mgm. per 100 cc.*	*mM. per liter*	*mM. per liter*	*mgm. per 100 cc.*				
6	0		26	5.9	109.4	9.8	0	0	0	
	53						+	0	0	Convulsion.
	70		204	8.5	113.6	10.2	+	0	0	
	82						+	+	0	
	84						+	+	+	
	113	+	391	11.9	98.4	6.7	+	+	+	Gradual decline to death.
7	0		27	5.1	108.6	10.9	0	0	0	Convulsion. Bloody diarrhea. Sudden loud cry, arrest of heart, dyspnea, death.
	70		185	7.7	112.0	11.0	+	0	0	
	126						+	+	+	
	141	+	375	20.4	105.4	9.7	+	+	+	
8	0		29	4.6	107.8		0	0	0	
	66		220	11.8	86.8		+	0	0	
	79						+	+	+	
	107						+	+	+	
	111	+	378	12.3						Death not observed.
10	0		24	4.6	104.6		0	0	0	
	73		161	11.8	93.6		+	+	0	
	91–93	+								Death not observed.
11	0		41	4.7	109.4		0	0	0	
	24			6.4	107.8	11.1	+	0	0	
	49			9.5	105.4		+	+	0	
	65		379	9.2	114.0		+	0	0	
	68						+	+	0	
	72						+	+	+	
	82–83	+				11.7	+	+	+	Death not observed.
	83			14.3	103.8	9.7				Blood 1 hour postmortem.
12	0		30	4.4	101.4	10.4	0	0	0	
	49						+	0	0	
	92		226	7.6	100.6	11.6	+	0	0	
	103						+	+	+	Cardiac failure, dyspnea, finally respiration stopped.
	106	+	354	12.4	103.6	11.2	+	+	+	
13	0		26	3.5	106.0		0	0	0	
	49						+	0	0	
	72		166	8.5	104.6		+	0	0	
	113						+	+	+	
	152	+	346	17.1	66.4		+	+	+	Gradual decline to death.

anuria, and in those with anuria receiving potassium. The range of terminal potassium concentration is the same in the three groups. In Figure 6 the rise in nonprotein nitrogen is plotted against the increase in serum potassium. There is no difference between the results with nephrectomized dogs (open circles) and those with dogs in which ureters were ligated (open squares). However, animals in which added potassium had been injected (solid circles and squares) had a lower blood nonprotein nitrogen at death than did the uninjected animals having equivalent increases in serum potassium. This fact, taken in conjunction with the demonstration in Figure 5 that animals in both series died with the same concentration of potassium, indicates that death is correlated with a certain degree of elevation of serum potassium rather than with a certain increase in the blood nonprotein nitrogen. This conclusion is further borne out in Figure 7, in which the times of survival of the animals in the various groups are plotted. There is no difference in the duration of life of nephrectomized animals and those with ligated ureters. There is, however, a striking decrease in the survival time of those receiving potassium. This might have been predicted from

TABLE II

Nephrectomized dogs, no K injected

Number	Time	Death	Blood NPN	Serum			Electrocardiographic findings			Remarks
				K	Cl	Ca	T wave changes	P waves disappear	QRS widening	
	hours		*mgm. per 100 cc.*	*mM. per liter*	*mM. per liter*	*mgm. per 100 cc.*				
N 1	0		39	5.6	107.0		0	0	0	
	65		192	8.9	98.4					
	72						+	0	0	
	147						+	+	0	
	148						+	+	+	Sudden groan, followed by
	152	+	411	15.3			+	+	+	death.
N 2	0		27	5.4	104.6		0	0	0	
	65		176	8.5	88.2					
	72						+	0	0	
	97						+	+	0	
	117						+	+	+	
	125	+	394	18.0			+	+	+	Sudden death.
N 3	0		50	4.8	107.8		0	0	0	
	65		211	9.6	90.8					
	72						+	0	0	
	95						+	+	0	
	100						+	+	+	Sudden death, preceded by
	116	+	378	16.0			+	+	+	dyspnea.
N 4	0		47	4.3	101.4		0	0	0	
	48			6.8	85.6	9.4	+	0	0	
	72		292	11.8	69.8		+	+	+	
	76	+	363	12.3	74.4	9.7	+	+	+	Sudden death.
N 6	0		44	4.8	98.2		0	0	0	Gradual cessation of respiration and heart. (Coarse ventricular fibrillation.)
	48						+	0	0	
	72		211	8.3	88.4	11.9	+	0	0	
	104						+	+	0	
	125						+	+	+	
	126	+	322	13.4	94.4	9.5	+	+	+	

the demonstration (Figure 5) that both groups have the same concentration of potassium at death.

(*B*) *Experiments with anuria due to the injection of mercuric chloride*

Eleven experiments in which mercuric chloride solution was injected are summarized in Table IV. Blood nonprotein nitrogen and serum potassium rose regularly and progressively, just as they did in the animals with surgically induced anuria. As in the other types of anuria, changes in the T wave of the type ascribed to potassium appeared early and regularly in these animals with the anuria of mercury poisoning. However, the group with mercury poisoning differs fundamentally from the nephrectomized group and from the group with ligated ureters in at least three respects: (*1*) In three of the five instances in which terminal serum potassium concentrations were determined, a concentration less than 10 mM. per liter was found. This is less than the minimal lethal concentration in normal animals. Of the five in which it was not determined, four died within twenty-four to thirty-six hours after the establishment of anuria. These four therefore probably had serum potassium concentrations well below 10 mM. per liter, if the same rate of increase of potassium concentration be assumed in these as in the other experiments. Thus, only two, or possibly three, out of eleven dogs could have had terminal concentrations of potassium compatible with death due to potassium poisoning. (*2*) P waves were retained in all but two experiments. In experiment Hg 8 P waves were retained and the QRS complex was not widened even at the very end. Electrocardiograms from one of the two exceptional instances (Hg 9) in which P waves did disappear are presented in Figure 8. (*3*) The survival time was

on the average much shorter than in dogs rendered anuric by surgical means (Figure 7). This is true in spite of a considerable variation in the time of survival, due in part to the different doses of mercury used in different experiments.

(C) *Clinical observations*

The results of chemical and electrocardiographic studies in five patients with advanced chronic pyelonephritis and glomerulonephritis are summarized in Table V. In all instances the serum

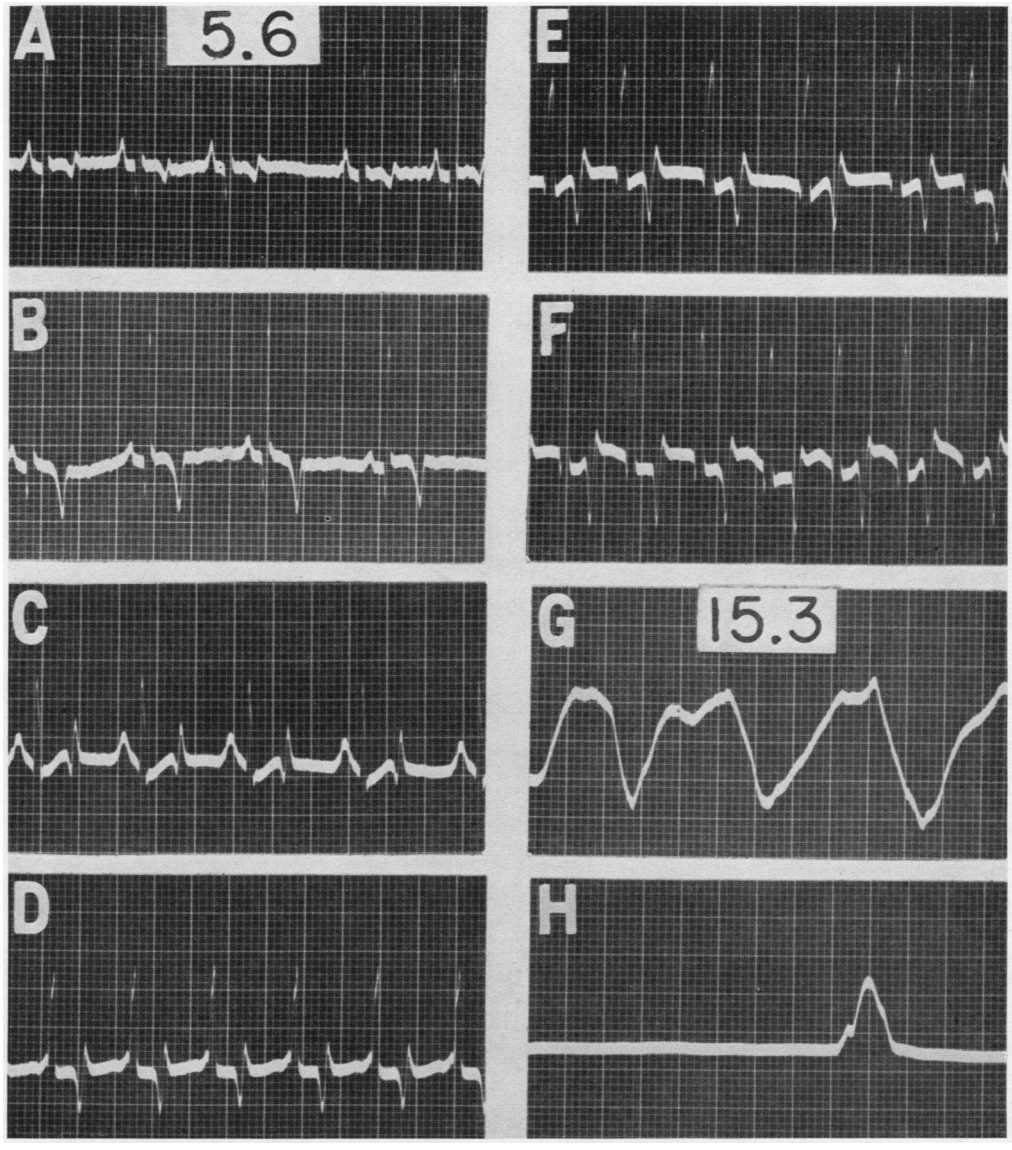

FIG. 2. NEPHRECTOMIZED DOG. NO KCl INJECTED

(A) Control, Lead II.
(B) 96 hours after nephrectomy. P waves still present. T waves inverted.
(C) 108 hours. P waves present, S–T segment depressed, T waves diphasic.
(D), (E), (F) 120 to 124 hours. P waves have disappeared, S–T segment depressed. QRS high but of normal width. Animal walking about.
(G) 125 hours. Complete disorganization of QRS complexes. Serum potassium 15.3 mM. per liter.
(H) 1 minute later. Death.

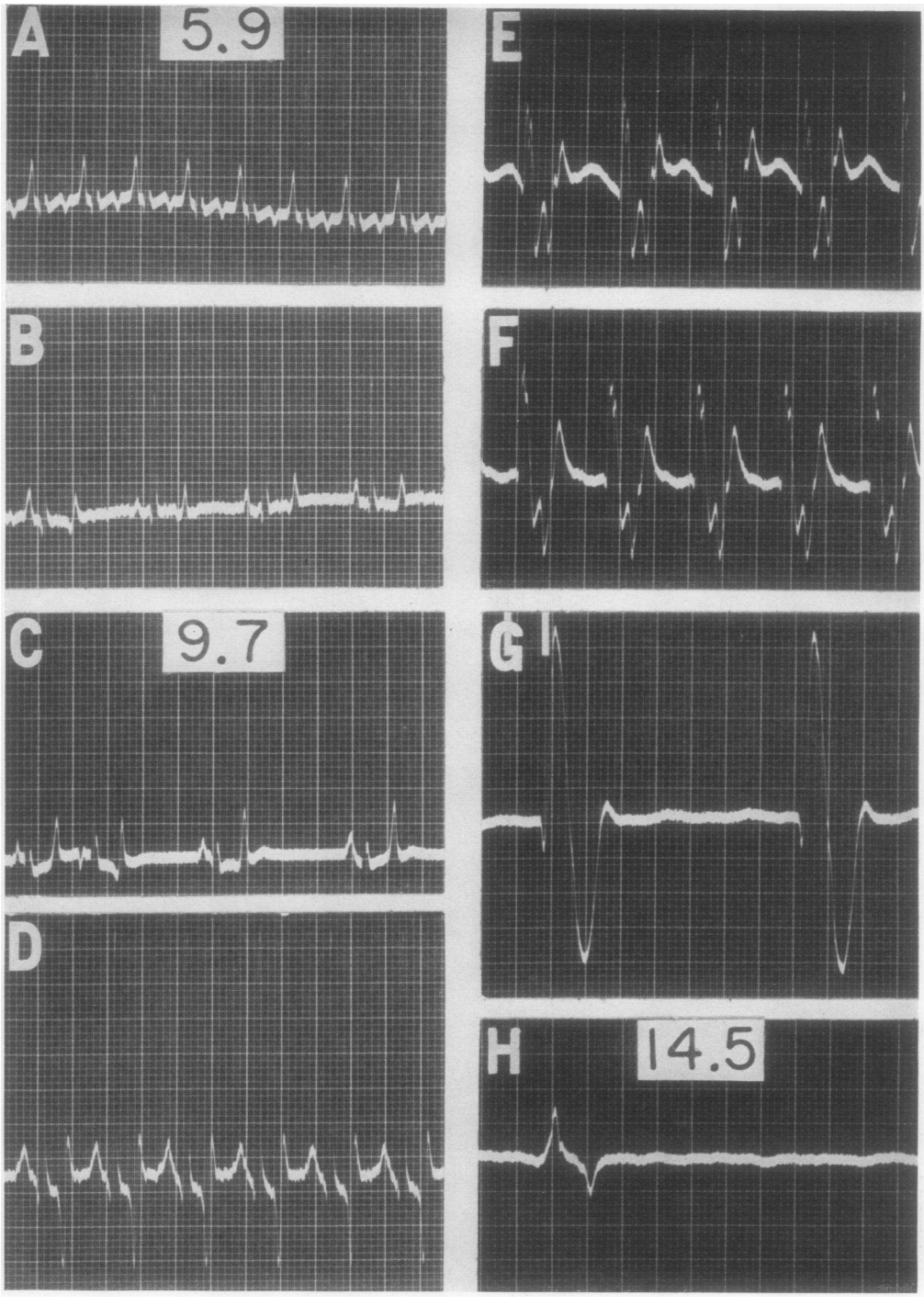

FIG. 3. URETERS TIED. NO KCl INJECTED

(A) Control, Lead II.
(B) 48 hours after operation. T waves slightly diphasic.
(C) 72 hours. P waves present. S–T depression. Serum potassium 9.7 mM. per liter.
(D), (E), (F) Series taken at intervals during 12 hours preceding death. Loss of P waves, widening of QRS complex, further T wave changes.
(G), (H) Terminal records, showing complete absence of P, and extreme intraventricular block. Serum potassium 14.5 mM. per liter.

TABLE III

Ureters tied or nephrectomized, KCl injected intravenously immediately following ligation

Number	Time after ligation	Amount of K injected isotonic	Death	Blood NPN	Serum		Electrocardiographic findings			Remarks
					K	Cl	T wave changes	P waves disappear	QRS widening	
	hours	*cc. per kilo*		*mgm. per 100 cc.*	*mM. per liter*	*mM. per liter*				
14	0	22.7		27	4.8	107.2	0	0	0	Died very suddenly having been walking about apparently normally 20 minutes before death.
	18				9.8	106.4	+	+	0	
	24						+	+	0	
	30		+	111	11.3	108.0				
15	0	less than 22.7*		32	5.1	104.4	0	0	0	
	21				6.8	106.4	+	0	0	Sudden death preceded by dyspnea.
	40						+	+	0	
	53						+	+	+	
	55		+	177	13.3	88.8	+	+	+	
17	0	20.0		29	4.1	103.2	0	0	0	Sudden death following 10 minutes of dyspnea.
	18				8.7	102.4	+	0	0	
	29						+	+	0	
	49						+	+	+	
	54		+	223	13.0		+	+	+	
20	0	20.0		29	5.4	108.0	0	0	0	
	18				8.8	101.6	+	0	0	
	29						+	+	0	Sudden death.
	40						+	+	+	
	42		+	187	12.9	101.6	+	+	+	
N 7	0	15.0		31[s]	5.0		0	0	0	? Sudden death.
	19			80[s]	7.4		+	0	0	Not actually observed.
	74						+	+	0	
	106						+	+	0	
	108		+	267	12.2					
N 8	0	15.0		33[s]	5.1		0	0	0	
	19			88[s]	9.3		+	0	0	Sudden dyspnea, then death.
	31						+	+	0	
	50						+	+	+	
	52		+	195	13.5		+	+	+	
N 9	0	15.0		36[s]			0	0	0	
	18			88[s]	5.6		+	0	0	
	73						+	+	+	Exact moment of death not observed.
	94						+	+	+	
	96		+	279	11.6					
N 10	0	15.0		29	5.2		0	0	0	
	10			48	5.4		+	0	0	
	67						+	+	0	
	68		+	216	14.5					Death not observed.
N 11	0	15.0		30	4.9		0	0	0	
	9			60	6.1		0	0	0	
	29						+	0	0	
	61						+	+	0	
	74						+	+	+	Death not exactly observed.
	80		+	264	14.8		+	+	+	

* Unknown amount of solution lost.
[s] Serum determination.

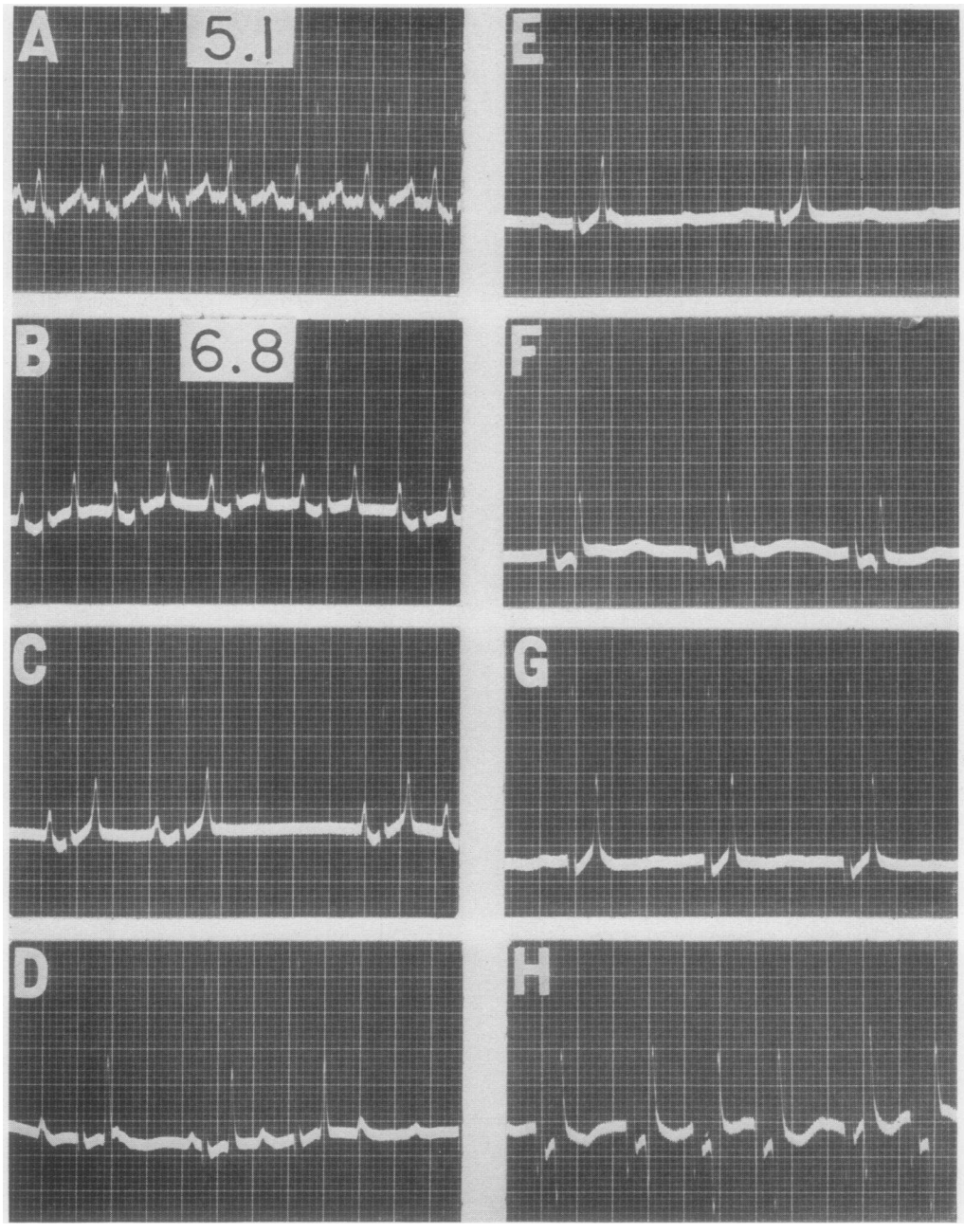

FIG. 4. URETERS TIED, KCl INJECTED INTRAPERITONEALLY IMMEDIATELY FOLLOWING LIGATION

(A) Control, Lead II.

(B) 21 hours after ligation. Little change. P waves present. Serum potassium 6.8 mM. per liter.

(C), (D), (E) 21 to 38 hours. Progressive diminution and widening of P waves. Some PR block. T waves become progressively higher.

(F) 40 hours. P wave has disappeared.

(G) 44 hours. Progressive increase in height of T; P remains absent. QRS complex intact.

(H) 55 hours. Beginning QRS widening. Death occurred 2 hours later. Serum potassium 13.3 mM. per liter.

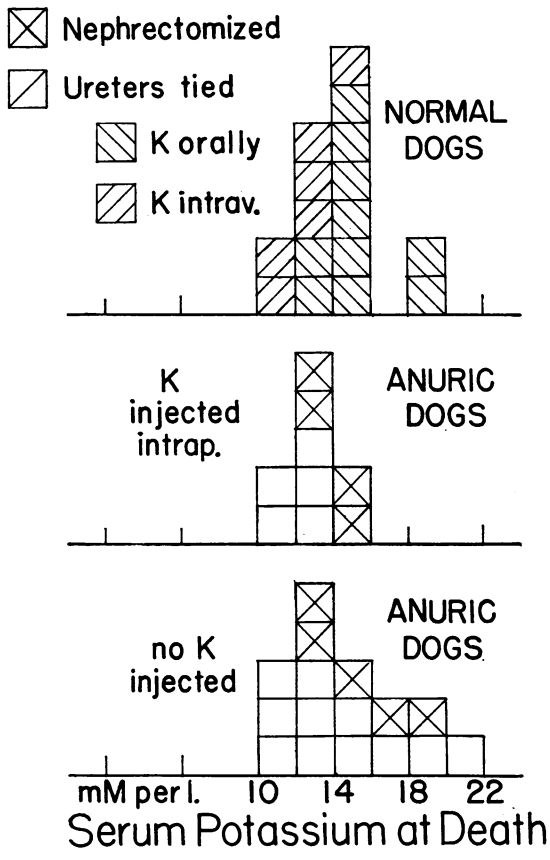

FIG. 5. CONCENTRATION OF POTASSIUM AT DEATH

Each square represents one experiment. There is evidently no difference between the concentration in the anuric experiments and in the controls. There is also no difference between the concentrations in the anuric experiments with potassium administration and those without potassium injection.

potassium concentration was but little elevated, although the blood nonprotein nitrogen was extremely high. The electrocardiograms showed no changes characteristic of potassium poisoning. This is true in spite of the fact that several of the electrocardiograms were taken just before death. One of these is shown in Figure 9, in which the last records were taken ten minutes before respiration ceased; P waves and QRS complexes are intact. The associated potassium concentration in serum was 6.9 mM. per liter.

DISCUSSION

Potassium regularly accumulates in the serum of anuric animals even when food is withheld and no potassium salts are injected. Since its rise roughly parallels that of the blood nonprotein nitrogen (Figure 6), it is reasonable to assume that it results from the same cause, *i.e.*, from the breakdown of body cells.[3] Such an explanation, of course, implies inability on the part of the body to excrete the potassium by any channel other than the kidney or to store any considerable amount. The variable rate of increase of the serum potassium, together with the fact that it may occasionally even drop for a time (Table I, experiment 3), indicates that the tissues may have some ability to store potassium. The generally progressive character of the increase, however, indicates that this capacity is strictly limited.

Winkler and Smith (33) observed that potassium injected into normal dogs distributes itself through a volume considerably larger than that of the extracellular fluid. Potassium was therefore under these circumstances able to enter cells and at least temporarily to be stored there. The present experiments with injections of potassium into anuric dogs indicate a similar large apparent volume of distribution. In Table VI apparent volumes of distribution of added potassium are calculated for all the experiments in which potassium was injected. (It is assumed that, after a period of twelve hours, absorption from the peritoneum is complete, yet potassium release from tissue breakdown is negligible.) Since the extracellular fluid corresponds only to about 25 per cent of the body weight, considerable potassium must have entered cells in these experiments. Especially striking are experiments N 9, N 10, and N 11, in all of which only a small fraction of the injected potassium could be accounted for in the extracellular fluid the next morning. In spite of this demonstrated capacity of potassium to leave the extracellular fluid to enter cells, the concentration in serum gradually rose in subsequent days until death ensued. Storage of potassium under these circumstances is therefore definitely limited in

[3] The ratio of the increase in serum concentration of nonprotein nitrogen to that of potassium in these experiments is about one gram per liter of the former for every 2 or 3 mM. per liter of the latter. Assuming their volumes of distribution to be similar, these concentrations are proportional to total amounts. The ratio is consistent with the hypothesis that all the increase in potassium and nitrogen is derived from tissue breakdown.

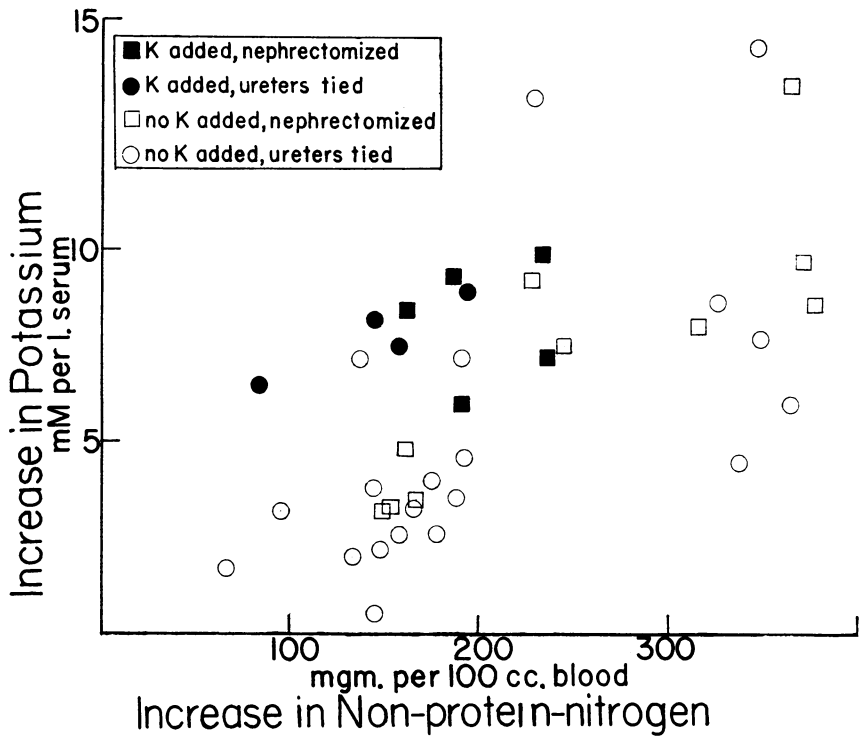

FIG. 6. INCREASE IN BLOOD NONPROTEIN NITROGEN (△ NPN) AND SIMULTANEOUS INCREASE IN SERUM POTASSIUM (△ K)

All blood samples in which these two determinations were carried out are included. The association is evident, but the points scatter rather widely.

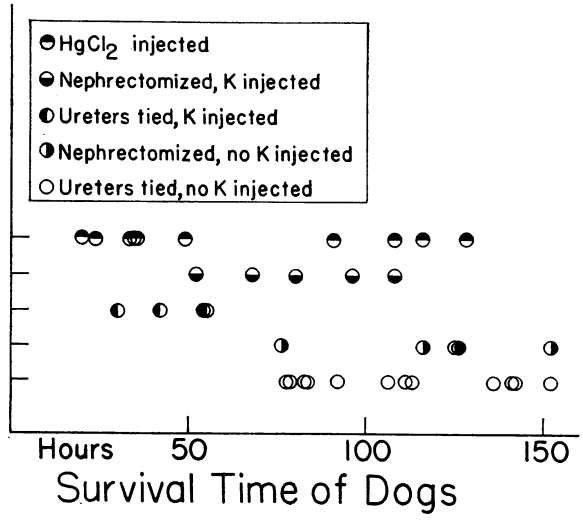

FIG. 7. SURVIVAL TIME OF THE ANIMALS IN DIFFERENT GROUPS OF EXPERIMENTS

Each circle represents one experiment. The time is estimated from the onset of anuria. The animals receiving potassium evidently die much sooner on the average than those receiving none. There is a wide dispersion of the experiments with mercury poisoning, but many of the animals died in a shorter period than did any of those with simple surgical anuria.

amount. No clue is available from these experiments concerning the form in which the potassium is stored in cells, nor is it clear whether it enters all cells or only certain specialized ones.

The survival of animals with surgically induced anuria until potassium attains a level in serum sufficient to produce death is only presumptive evidence that potassium is the effective lethal agent. More conclusive is the fact that serial electrocardiograms invariably demonstrate a sequence identical with that produced by experimental potassium poisoning. That the electrocardiographic sequence in anuria is truly due to potassium is confirmed in a negative way by the studies of human subjects with uremia, in which the serum potassium was not elevated in spite of the high concentration of nonprotein nitrogen and of other products in the blood. In such patients no electrocardiographic changes of the sort observed in experimental anuria could be found. It was observed in the animals that the terminal cardiac slowing and arrest occurred quite suddenly, although blood pressure and cardiac output had presumably been well maintained. This mode of

TABLE IV

Mercury poisoning

Number	Time after injection	Amount $HgCl_2$ given	Death	Blood NPN	Serum K	Electrocardiographic findings			Remarks
						T wave change	P wave out	QRS widening	
	hours	*mgm. per kgm.*		*mgm. per 100 cc.*	*mM. per liter*				
Hg 2	0	4.0		41	5.7	0	0	0	
	24					+	0	0	
	30					+	0	0	
	30–38		+						Not observed.
Hg 3	0	4.0		24	5.7	0	0	0	
	24					+	0	0	
	73				7.8	+	0	0	
	89				9.0	+	+	0	
	90			352	10.2	+	+	+	
	90–91		+						Not observed.
Hg 4	0	4.0		42	5.6	0	0	0	
	24					+	0	0	
	30					+	0	0	
	30–38		+						Not observed.
Hg 5	0	4.0		33	5.1	0	0	0	
	24					+	0	0	
	48					+	0	0	
	48–49		+	166	6.0				Not observed.
Hg 7	0	3.5		28		0	0	0	
	21					+	0	0	
	80				7.1	+	0	0	
	104					+	0	0	
	104–112		+						Not observed.
Hg 8	0	3.5		125	6.9	0	0	0	Gradual disappearance of respirations; sudden ventricular flutter and then coarse fibrillation.
	20		+	184	9.2	+	0	0	
Hg 9	0	3.5		33	6.1	0	0	0	
	22					+	0	0	Short period of dyspnea, then sudden death.
	80			317	9.8	+	0	0	
	92					+	+	0	
	94					+	0	0	
	116		+	370	13.2	+	+	+	
Hg 10	0	3.5		34		0	0	0	
	20					+	0	0	
	22–26		+						Not observed.
Hg 11	0	3.0		34	6.2	0	0	0	
	20					+	0	0	
	78				10.5	+	0	0	
	121+		none			0	0	0	Recovered.
Hg 12	0	3.0		30	5.6	0	0	0	
	20					+	0	0	
	79				6.4	+	0	0	
	128		+	387	9.3	+	0	0	Died suddenly.
Hg 13	0	3.0		24		0	0	0	
	20					+	0	0	
	30					+	0	0	
	30–40		+						Not observed.

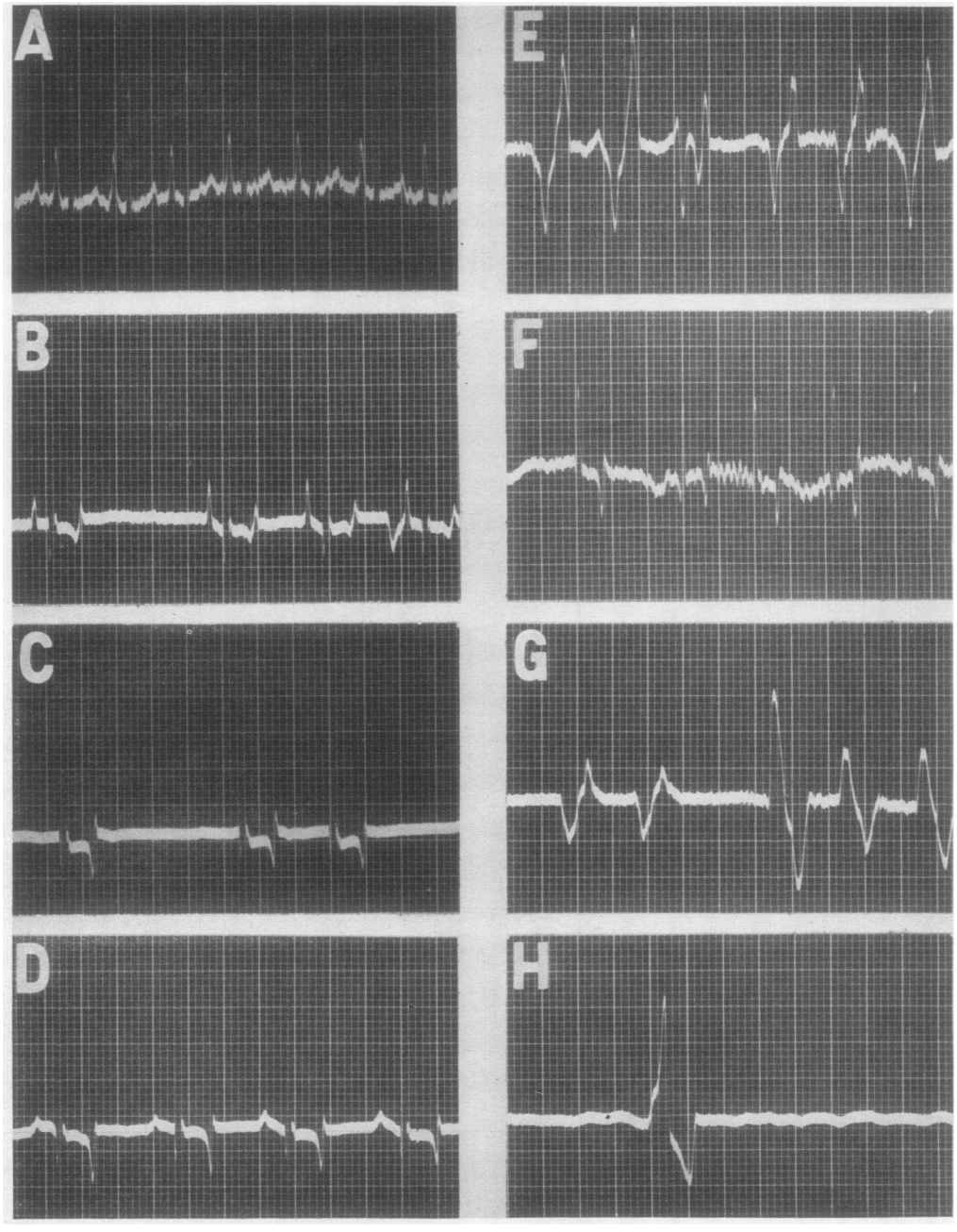

FIG. 8. MERCURY POISONING

(A) Control, Lead II.
(B) 30 hours after injection of mercury. T wave diphasic.
(C) 92 hours. P waves have disappeared, drop in S–T segment.
(D) 102 hours. P waves return temporarily.
(E), (F), (G) 116 hours. Animal dyspneic. P waves have again disappeared, T waves very large, QRS complexes widening and disorganizing.
(H) A few minutes later, at moment of cessation of respiration. Serum potassium 13.2 mM. per liter.

TABLE V

Summary of clinical observations

Number	Diagnosis	Date	Potassium of serum	Blood NPN	Remarks
			mM. per liter	*mgm. per cent*	
80838*	Chronic pyelonephritis	Spetember 12, 1940	6.9	208	Died 10 minutes later.
A 3408	Chronic pyelonephritis	August 27, 1940 morning evening	 6.7 6.5	 256 225	Anuric for preceding 2 or 3 days. Died 2 hours after second blood sample.
B 1929	Chronic glomerulonephritis	April 18, 1940 July 13, 1940	5.0 5.8	122 253	Died 12 hours later.
A 90560	Chronic glomerulonephritis	August 28, 1940	3.8	190	Convulsions at this time. Died 14 days later.
B 5156	Chronic glomerulonephritis	September 29, 1940	5.4	118	Still living.

* See Figure 9 for electrocardiograms in this case.

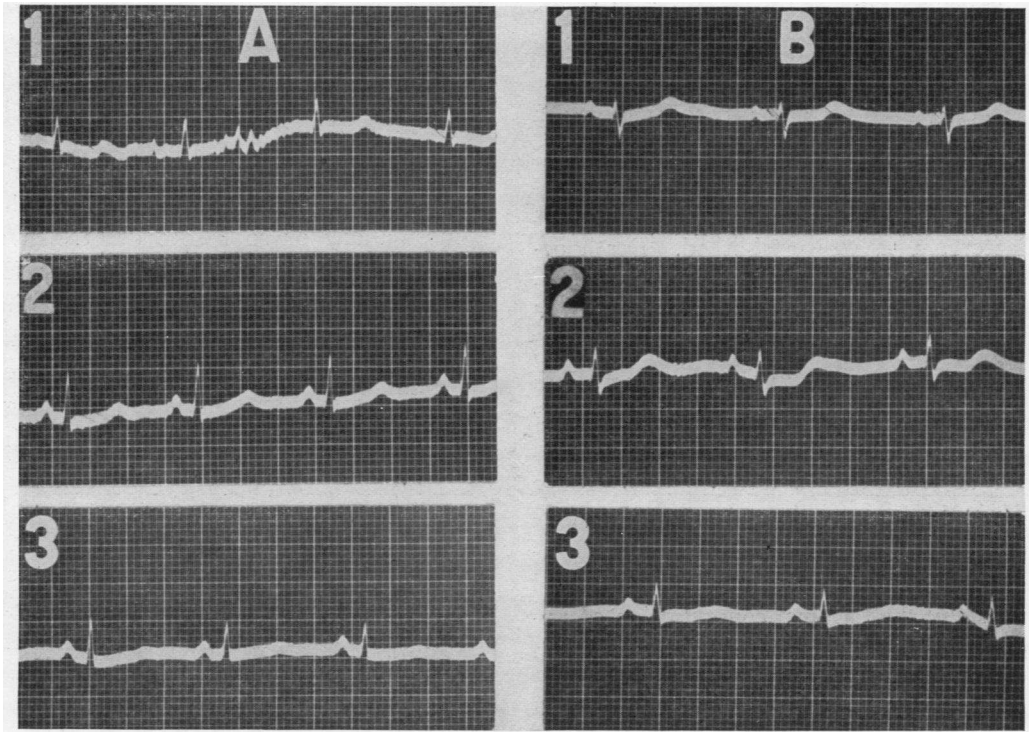

FIG. 9. ELECTROCARDIOGRAMS FROM A YOUNG PATIENT WITH LONG-STANDING CHRONIC PYELONEPHRITIS, JUST BEFORE DEATH

Numbers refer to the respective leads. (A) 24 hours before death; (B) 10 minutes before death. The serum potassium was 6.9 mM. per liter and the blood NPN 208 mgm. per cent just before death. Note that in (B) the P waves are still present and the T waves show no characteristic changes.

TABLE VI

Apparent volumes of distribution

Experiment	Increase in potassium concentration (A)	Amount of potassium injected (B)	Apparent volume of distribution of potassium $\frac{(B)}{(A)} \times 100$
	*mM. per liter serum water**	*mM. per liter body weight*	*per cent of body weight†*
U 14	5.4	3.50	65
U 17	5.0	3.08	62
U 20	3.7	3.08	83
N 7	2.6	2.31	89
N 8	4.5	2.31	51
N 9	1.0±	2.31	very large
N 10	0.2	2.31	very large
N 11	1.3	2.31	178

* Assuming serum water = 93 per cent of serum.
† Assuming 1 liter = 1 kilo.

death is entirely consistent with that due to potassium poisoning (2). The alternative possibility is that some other substance retained in the body to the same extent as potassium might be the true cause of death, the rise in potassium with its correlated electrocardiographic changes being a non-essential accompaniment. This seems, however, adequately ruled out by the experiments in which added potassium was introduced into the system after anuria was established. Death occurred in the same way with the same electrocardiographic sequence and at the same range of concentration of potassium as in the control series, but at a much earlier time and with distinctly less elevation of blood nonprotein nitrogen. Other workers (34, 35) have reported that diets high in potassium decrease the survival time of anuric rats. Were death really dependent on the accumulation of some toxic substance other than potassium, the time of death would not be accelerated in this way and the terminal concentration of potassium would be expected to be higher than usual.

Altogether, the evidence seems conclusive that death in surgical anuria is caused by cardiac poisoning due to the accumulation of excessive potassium in the body fluids. The difficulty of generalizing concerning other forms of anuria is evident from the experiments with mercury poisoning. Here anuria occurred and potassium of serum rose, as in the other experiments. However, before the potassium reached levels sufficient to cause death and before electrocardiograms showed more than the earlier signs of potassium effect, the animals usually died. The cause of death is uncertain, but it clearly was not potassium poisoning. It may be conjectured that if the animals with mercury poisoning had lived as long as did the dogs rendered anuric by surgical means, they too might have died of potassium poisoning. This may have been the case in the two instances in which P waves disappeared and the terminal serum potassium concentration was greater than 10 mM. per liter. Since most of them did not live so long, potassium poisoning in mercurial anuria must be considered as a limiting cause of death, which is ordinarily not operative, as some other factor is usually responsible for death before sufficient potassium has accumulated.

The clinical studies demonstrate clearly that potassium poisoning is not the usual cause of death in terminal nephritis, since neither elevation of concentration of potassium nor cardiac damage detectable by the electrocardiogram was sufficient to cause death. This is undoubtedly correlated with the fact that even in very advanced nephritis anuria does not usually occur until a few hours or at most a day or so before death. In another study of patients with nephritis Winkler, Hoff and Smith (3) found that amounts of potassium sufficient to keep the serum concentration nearly normal were excreted even when clearances were much depressed. In other words, so long as the nephritic subject excretes any urine at all he eliminates appreciable amounts of potassium, so that the accumulations observed in experimental anuria are not apt to occur. The possibility may be considered that potassium may be the cause of death in those occasional nephritic patients with persistent extreme oliguria or anuria, but such cases have not been encountered in the course of the present study.[4] The high concentrations of potassium in serum occasionally reported in nephritis probably originate from extreme oliguria and some of the recorded values are certainly high enough to be in themselves dangerous to the heart (23).

[4] Dr. Daniel Darrow has observed one child with acute glomerulonephritis and extreme oliguria for several days. His serum potassium shortly before death was 9.3 mM. per liter. No electrocardiograms were obtained.

CONCLUSIONS

1. The concentration of potassium in the blood serum increased regularly and progressively in animals rendered completely anuric. This increase results from the breakdown of the animal's own tissues, together with the restricted ability of the organism to store potassium.

2. Serum potassium continues to increase in dogs rendered anuric by ureteral ligation or nephrectomy until cardiac arrest due to potassium poisoning occurs. Thus potassium poisoning is the usual effective cause of death in animals so treated.

3. Dogs rendered anuric by mercuric chloride injections usually die of some unknown cause before the concentration of potassium rises sufficiently to cause cardiac arrest.

4. Elevation of serum potassium with consequent cardiac arrest is not the usual cause of death in patients with chronic nephritis and terminal uremia.

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