or more urea and in an acidic medium (pH 6). 3. Incorporation of 2% NH_4Cl as a urinary acidifier in the diet of rats did not have a major effect on the nitrofurantoin concentrations attained in the urine or on the total amount of nitrofurantoin excreted. 4. The ingestion of a high protein diet by albino rats to increase urea excretion did not adversely affect the urinary concentration nor the total amount of nitrofurantoin excreted. 5. Albino rats receiving 0.1% nitrofurantoin (about 10 × calculated human dose) and 2% NH_4Cl in the diet for a 2-week period showed no evidence of crystalluria or kidney pathology.

We wish to thank Dr. Meredith Gardiner for supervising the preparation of the kidney sections and examining them for pathology. We also wish to thank Dr. Paul Newland of the Medical Department for supervising the study in which the four 100 mg tablets of nitrofurantoin were administered to each of 9 normal individuals.

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Effect of Renal Ischemia on Anaerobic CO_2 Production by Dog Kidney *in vitro*.* (32247)

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The studies of Trueta, Barclay, Daniel, Franklin and Pritchard(1) demonstrated that renal cortical ischemia may be produced by a variety of humoral and neurogenic phenomena such as: hemorrhage, catecholamine injection, tourniquet compression of a limb and electrical stimulation of the renal nerves (1,2). More recently, associated changes in specific functional and metabolic activities of the kidney have been identified: Gomori(3) reported that, in dogs subjected to electrical stimulation of the renal hilus while undergoing an osmotic diuresis, there were marked

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decreases in both effective renal plasma flow and GFR,‡ resulting in anuria. In addition, the extraction of PAH and the tubular transport maxima (T_m) for glucose and for PAH were depressed below pre-stimulation levels. The rates of *in vivo* renal oxygen consumption ($\dot{Q}O_2$) of ischemic kidneys are also significantly reduced below control levels(4). That the reductions in E_{PAH}, T_m glucose and T_m PAH are due to a fall in aerobic metabolism have not been clearly established. Indeed, the exact mechanism(s) by which renal ischemia induces these metabolic and/or functional alterations in the kidney is not known.

We recently published studies showing that washed homogenates and slices of dog kidney have the capacity to produce CO_2 anaerobically when incubated with α-ketoglutarate (α-KG) and oxaloacetate (OAA)(5). The major reaction which accounts for this anaerobic CO_2 production was shown to be: α-KG + OAA + GDP + P_i → Succinate + Malate + GTP + CO_2 (Reaction I).

During this study it was noted that the dog kidneys obtained for these experiments could be categorized into two groups: (a) those kidneys with pale or blanched cortices which were considered to be "ischemic," and (b) those kidneys with pink or normal cortices which were considered to have been adequately perfused at the time of nephrectomy. The blanched kidneys of group (a) were obtained from dogs which appeared more excited prior to administration of the anesthetic or from dogs in which the induction of anesthesia was associated with some excitement.

In group (a), the paleness began at the cortico-medullary border and radiated outward to the surface of the cortex. The gross color of the cortices of these kidneys resembled descriptions of cortical ischemia(1,2). No paleness was ever noted in the medullary region of this group of kidneys. The pink cortices of group (b) kidneys served as the source of tissue for the observations made in our earlier report(5).

We are now reporting the anaerobic CO_2 production rate studies done with washed cortical homogenates and slices prepared from all of the blanched or ischemic kidneys. These latter washed homogenates show a large metabolic difference from homogenates of non-ischemic kidneys in that the rate of anaerobic CO_2 production (from Reaction I) is markedly lower. Further definitive enzymic studies have elucidated a possible mechanism by which ischemia induces the change in the rate of anaerobic CO_2 production by homogenates. This change in enzymic activity could limit the rate of energy production by the cortex and thus may underlie some of the alterations in renal function which occur following renal ischemia.

Methods. All studies were done with kidney tissue taken from fasted (12 hr), anesthetized, male and female mongrel dogs weighing between 10 and 20 kg. The dogs were anesthetized with sodium pentobarbital (30 mg/kg) which was administered IV or IP; in several experiments, pentobarbital (60 mg/kg) was administered orally. Associated with the oral administration of pentobarbital was a lower incidence of renal cortical ischemia. In all cases, supplemental doses of the anesthetic were administered IV when necessary.

Within 15-20 minutes after induction of anesthesia, bilateral nephrectomy was performed through a midline abdominal incision. The kidneys were immediately packed in ice, following which cortical and medullary segments were separated and homogenates or slices of tissue were prepared as described previously(5). Anaerobic metabolic studies were done simultaneously on both

‡ The following abbreviations are used in this report: α-KG: α-ketoglutarate; OAA: oxaloacetate; TRBF: total renal blood flow; ERPF: effective renal plasma flow; GFR: glomerular filtration rate; PAH: para-aminohippurate; E_{PAH}: renal extraction of PAH; T_m: maximal tubular transport rate; Q_{O_2}: oxygen consumption rate; P_i: inorganic phosphate; GTP: guanosine triphosphate; GDP: guanosine diphosphate; IV: intravenously; IP intraperitoneally; M±SE: mean ± standard error of mean; NAD^+: oxidized form of nicotine adenine dinucleotide.

The following enzyme abbreviations are used in this report as recommended by the Enzyme Commission of the International Union of Biochemistry (12): α-KG-DH: 2-oxoglutarate: lipoate oxidoreductase (EC 1. 2. 4. 2); malic-DH: L-malate: NAD^+ oxidoreductase (EC 1. 1. 1. 37).

TABLE I. CO_2 Production by Cortical and Medullary Washed Homogenates of Ischemic and Non-Ischemic Kidneys.

Homogenate preparation from:	CO_2 production rate, μmoles/100 mg dry wt hr	
	Cortex	Medulla
Non-ischemic kidney	14.6 ± 1.8 (8)	1.3 ± .4 (6)
Ischemic kidney	6.0 ± 3.0 (7)	.9 ± .6 (6)

Values are means ± SE. Number of experiments shown in parentheses. The difference between cortical ischemic and cortical non-ischemic preparations is statistically significant at 95% level of confidence ($P < 0.05$). The difference between medullary ischemic and non-ischemic preparations is not statistically significant ($P > 0.5$). Rates of CO_2 production by medullary homogenates are not significantly greater than zero (non-ischemic, $P > 0.3$; ischemic, $P > 0.4$).

cortical and medullary preparations. In a few experiments only cortical tissue was used so that a larger number of observations could be made from this region of the kidney in a single experiment (Tables I and II). All preparations were incubated in Warburg flasks at 30°C in an atmosphere of 95% N_2, 5% CO_2 with 8-33 mM Na α-KG, 33-42 mM NaOAA and either a bicarbonate-CO_2 buffer system for homogenates or Krebs-Henseleit medium for slices. A complete description of all materials, methods, and experimental protocols may be found in our earlier study(5).

Three types of experiment were done: 1) manometric studies in which the rate of anaerobic CO_2 production by washed homogenates or slices was determined; 2) chemical balance studies in which the changes in concentration of the products and reactants of Reaction I were quantified to determine the stoichiometry of Reaction I in homogenates (1 experiment) and slices (5 experiments); and 3) quantitative studies of the cortical and medullary activities of α-ketoglutarate dehydrogenase (α-KG-DH)‡ and malic dehydrogenase (malic-DH), the two dehydrogenases involved in Reaction I. These latter studies were done to determine the basis for the difference in activity of Reaction I in ischemic and non-ischemic kidney preparations. The method used for assaying these dehydrogenases was that of Quastel(6) in which ferricyanide is used as the electron acceptor under anaerobic conditions(5).

Results. From a total of 30 dogs, the kidneys of 12 were considered to have blanched cortices. Of these 12, 7 were used for anaerobic CO_2 production studies by washed homogenates and 5 were used for anaerobic CO_2 production studies by slices. All kidneys, blanched or unblanched, were studied; none was discarded. The anaerobic CO_2 production studies by unblanched kidneys from 18 dogs have been reported previously(5).

A. Anaerobic metabolism of cortical and medullary homogenates prepared from ischemic and non-ischemic kidneys.

1. *Anaerobic CO_2 production.* Washed homogenates of cortex, prepared from non-ischemic kidneys and incubated with either 33 mM or 42 mM NaOAA and 8 mM Na α-KG, produced 14.6 ± 1.8 μmoles CO_2/100 mg dry wt hr (M ± SE) (Table I)(5). No significant difference in rate of CO_2 production was observed when 33 mM OAA was substituted for 42 mM OAA. In contrast, washed homogenates prepared from ischemic cortices yielded only 6.0 ± 3.0 μmoles of CO_2. The difference in rate of CO_2 production between these two preparations is statistically significant. No significant difference in the mean rate of CO_2 production between medullary homogenates prepared from ischemic and non-ischemic kidneys was observed. Thus, the change in rate of anaerobic CO_2 production associated with cortical ischemia is limited to cortical tissue. However, since the rate of CO_2 production by medullary preparations from non-ischemic kidneys is not significantly different from zero, only an increase in the rate of CO_2 production by

TABLE II. CO_2 Production by Slices of Ischemic and Non-Ischemic Kidneys.

Slice preparation from:	CO_2 production rate, μmoles/100 mg dry wt hr	
	Cortex	Medulla
Non-ischemic kidney	16.7 ± 1.5 (10)	1.86 ± .74 (2)
Ischemic kidney	15.0 ± 2.2 (5)	0 (1)

The difference between non-ischemic and ischemic preparations is not statistically significant ($P > 0.5$).

medullary homogenates from ischemic preparations would have revealed a significant effect of ischemia by this technique.

We had previously shown in chemical balance studies with non-ischemic cortical and medullary tissue that the rate of anaerobic CO_2 production reflects the rate of Reaction I(5). In a single chemical balance study with an homogenate from an ischemic kidney, we observed the same 1:1:1 stoichiometry among the rates of α-KG utilization and the rates of CO_2 and malate production as had been seen using cortical homogenates from non-ischemic tissue. However, consistent with the decreased CO_2 production by the ischemic homogenate, there were markedly smaller (and similar) α-KG utilization and malate production rates. The medullary homogenates prepared from ischemic kidney showed the same low activity previously observed with non-ischemic medullary homogenates(5). Thus it appears that some component of cortical homogenates is sensitive to cortical ischemia.

2. *Activities of specific dehydrogenases in cortex and medulla.* In non-ischemic kidneys the activity of malic-DH in medullary homogenates has been shown to be quite low in comparison to its high activity in cortical homogenates. In contrast, the activity of α-KG-DH is approximately the same in both cortical and medullary homogenates(5). Thus, the low activity of malic-DH in the medulla may explain, at least in part, the low rate of anaerobic CO_2 production in the non-ischemic medulla.

A comparison of the activities of malic-DH and of α-KG-DH in ischemic and non-ischemic cortical homogenates is illustrated in Fig. 1. The activity of malic-DH in ischemic homogenates was 0.14 ± 0.01 μmole CO_2/100 mg dry wt min (M ± SE) while the activity in non-ischemic homogenates was 0.67 ± 0.21 μmoles CO_2. This difference in malic-DH activity between ischemic and non-ischemic tissue is statistically significant. Thus, with respect to Reaction I, renal ischemia changes the cortical enzyme activity pattern to that of the medulla.

Since malic-DH activity is present in both the cytoplasm and the mitochondria of cells,

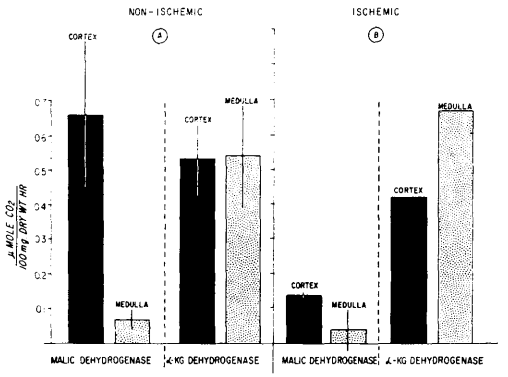

FIG. 1. Initial velocities in assays of α-KG and malic dehydrogenases in ischemic and non-ischemic homogenates. A = Non-ischemic Preparations; B = Ischemic Preparations. One ml aliquots of ischemic or non-ischemic washed homogenates were incubated anaerobically in Warburg flasks containing either α-KG or malate (8 mM) and an optimal concentration of ferricyanide(5) in 0.033 M $NaHCO_3$. Total CO_2 production was determined, plotted against time and the initial velocity was calculated from the slope of the curve; only the initial linear portion of the curve was used for slope determinations. The rates of control CO_2 production were subtracted from the experimental values. Boiled homogenates were substituted for viable homogenates in the control flasks. The number of experiments which make up this Figure are: a) α-KG-DH (non-ischemic) 3, (ischemic) 1; b) malic-DH (non-ischemic) 3, (ischemic) 2. The difference in activity of malic-DH in ischemic and non-ischemic cortical homogenates is statistically significant ($0.02<P<0.05$).

we determined whether the malic-DH activity in both supernatant and particulate fractions of kidney homogenate were affected by ischemia. Fig. 2 shows that it is only the activity of malic-DH in the particulate fraction of cortical homogenates which is depressed by ischemia: the activities of malic-DH in supernatant fractions of cortical and medullary homogenates are the same in both ischemic and non-ischemic homogenates. Thus, the cortical localization of the change in malic-DH activity is further limited to the mitochondria. It should be noted that the particulate fraction is also the site of low malic-DH activity in the medulla of non-ischemic kidneys(5).

Several explanations may be proposed for the inability of ischemic cortical homogenates to activate Reaction I if one assumes that the activity of malic-DH in the particulate fraction of cortical homogenates is the limiting factor for this reaction: (a) an inhibition

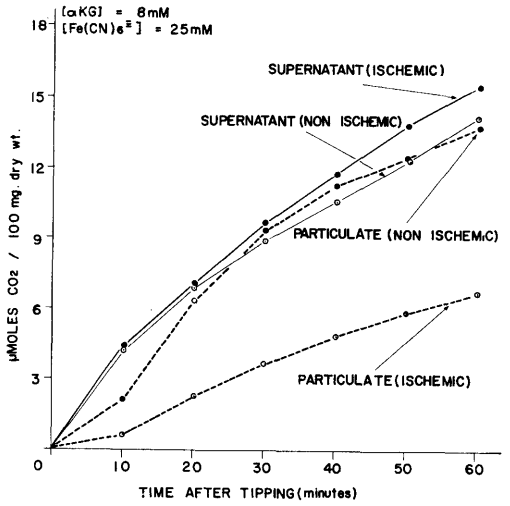

FIG. 2. Effect of ischemia on the activities of malic-DH in supernatant and particulate fractions of cortical homogenates: washed cortical homogenates of ischemic and non-ischemic kidneys were assayed for malic-DH. The supernatant of these homogenates was prepared for assay of malic-DH as described previously(5), and the activity was compared with that of particulate fractions. Total CO_2 production was plotted against time. The data in this Figure represent 2 experiments: 1 ischemic homogenate and 1 non-ischemic homogenate.

or inactivation of malic-DH may have occurred, (b) an increase in the permeability of mitochondrial membrane to malic-DH may have occurred with subsequent loss of the enzyme from this site in the tissue, or (c) the technique of homogenization of ischemic tissue may be contributing to the change in its malic-DH activity. Which of these suggestions best explains the mechanism of change in malic-DH activity may be determined by comparing the activity of Reaction I in slices of ischemic and non-ischemic kidneys. If an inactivation of malic-DH is present, then a depression in activity of Reaction I in the slice would be anticipated. Similarly, if there is a specific loss of malic-DH enzyme protein from the mitochondria prior to nephrectomy, a decrease in activity of Reaction I would be observed in the slice. On the other hand, if the technique of homogenization plays a critical role in our observations, then CO_2 production rate should be the same when either ischemic or non-ischemic slices are used. If the latter were the case, then the low activity of malic-DH observed in ischemic cortical homogenates could be attributed to a combination of ischemia and homogenization.

B. Anaerobic metabolism of cortical and medullary slices prepared from ischemic and non-ischemic kidneys.

1. *Anaerobic CO_2 production by slices.* Cortical slices prepared from non-ischemic kidneys, incubated anaerobically in Krebs-Henseleit medium with 8 mM Na α-KG and 33 mM NaOAA(5) at 30°C, produced 16.7 $\pm$ 1.5 μmoles CO_2/100 mg dry wt hr (M $\pm$ SE) (Table II); cortical slices from ischemic kidneys produced 15.0 $\pm$ 2.2 μmoles CO_2. No difference in rates of CO_2 production was noted in slices of medulla prepared from ischemic and non-ischemic kidneys. Thus, ischemia manifests its effect on anaerobic CO_2 production only in the washed homogenate, and not in the slice.

2. *Anaerobic chemical balances in slices.* In chemical balance studies no significant difference in the ratio of rate of CO_2 production : malate production : α-KG utilization between cortical slices prepared from ischemic and non-ischemic kidneys was observed (Fig. 3). Thus, in both the non-ischemic and the ischemic slice, other reactions in addition to Reaction I contribute to the total rate of anaerobic CO_2 production(5).

These results are consistent with the suggestion above that there is a specific alteration in the mitochondria obtained from ischemic cortical tissue. The ischemia may be considered to sensitize the mitochondria to subsequent homogenization, resulting either in: a) a specific increased permeability of the mitochondria to malic-DH, or to a cofactor essential for the activation of mitochondrial malic-DH, or b) an inactivation of the mitochondrial malic-DH.

Discussion. While many of the effects of renal cortical ischemia on renal function are well documented(3,4,7,8) the specific mechanism by which organ and cell function are changed is not understood. The ischemia may directly alter discrete transport mechanisms by which the kidney regulates body fluid volume and composition. On the other hand, ischemia may alter the free energy production which must be coupled to the

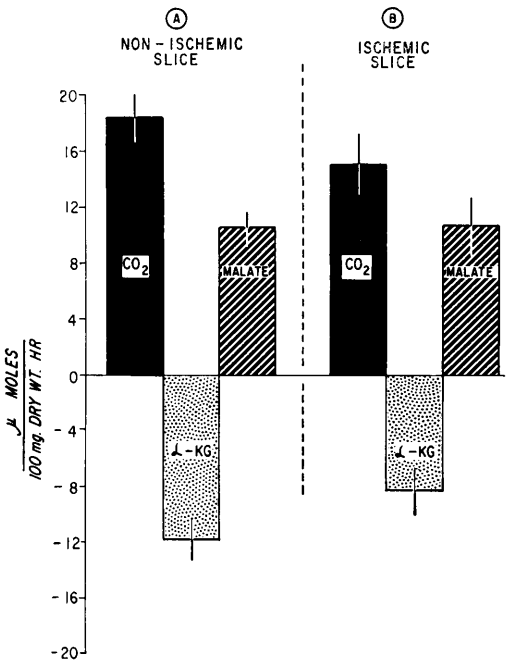

FIG. 3. Chemical balance study in slices based on Reaction I: A = Non-ischemic Preparations; B = Ischemic Preparations. Rates of CO_2 and malate production rates of α-KG utilization for each group are not significantly different from one another. Number of experiments included in this figure are: non-ischemic preparations (A) = 7; ischemic preparations (B) = 5.

work done by the several transport mechanisms. The observations made in this study demonstrate that the anaerobic rates of α-KG utilization and malate production by washed homogenates of dog kidney cortex are decreased by ischemia. The change in reaction rate has been postulated to be due to a decrease in malic-DH activity, while the activity of α-KG-DH is unaffected by ischemia. In contrast, both the rate of CO_2 production and the rate of Reaction I, as determined by chemical balance studies in cortical slices, are the same when prepared from either ischemic or non-ischemic tissue. Thus, we may have identified a latent metabolic change in the cortex which is induced by ischemia.

It should be noted that no quantitative data were obtained in our studies as to the degree of change in renal blood flow rate or the exact time interval over which the decreased blood flow rate persisted. Indeed, our identification of an "ischemic" or "non-ischemic" kidney is at best qualitative. However, the associated metabolic changes are so consistent and striking that cortical ischemia seems, as a first approximation, the most likely cause. From the experimental design, the period of ischemia was probably limited to a 15-30-minute period from just prior to the induction of anesthesia to the time of nephrectomy. In any case, the probable short period of renal ischemia which occurred in our experiments apparently poises the organ for the manifestation of a profound metabolic defect, *i.e.*, the marked decrease in the mitochondrial malic-DH activity and in the rate of CO_2 production in washed homogenates which may be associated with other reported metabolic changes due to renal ischemia(9). Whether the change in malic-DH activity is one of the first alterations in renal metabolism to occur in ischemia remains to be determined.

That slices from ischemic kidneys have the same rates of CO_2 production as slices from non-ischemic kidneys also indicates that the effect of the ischemia which we are studying is relatively subtle and may be one of the earlier alterations in renal metabolism due to ischemia. It should be noted that Emmel(10) observed significant morphological changes in renal cortical mitochondria after only 30 minutes of renal arterial occlusion: the cortical mitochondria changed in shape from rods to spheres. In contrast, most studies reported in the literature have not demonstrated any changes in renal enzyme activity prior to 2-5 hours of induced total ischemia(11). This would be consistent with our observations in the slice. However, since mitochondrial morphology does change after 30 minutes, it is conceivable that some of these intact, but altered, mitochondria would be more friable and more subject to changes in their permeability characteristics. Then, if homogenization occurs, more profound changes in the mitochondrial permeability to malic-DH or one of its cofactors may occur resulting in a loss of malic-DH activity.

If enzymes such as malic-DH are altered in structure or activity or are lost from mitochondria due to ischemia, then this change

in malic-DH activity could explain the lower rates of oxygen consumption reported by Dole *in vivo*(4) and Schirmer *in vitro*(9). Further, if energy from oxidation of substrates is limited by this decrease in malic-DH activity, one could also explain the depressed T_m for PAH and for glucose. Whether a loss in activity of malic-DH by ischemic kidneys does indeed explain the depressed rate of O_2 consumption of cortical slices(9) awaits further investigation.

Summary. 1) Rates of anaerobic CO_2 production by tissue obtained from dog kidneys with evidence of cortical ischemia have been compared with tissue from non-ischemic kidneys. Anaerobic CO_2 production rate was consistent with the following coupled oxidation-reduction reaction: α-ketoglutarate + oxaloacetate + GDP + P_i → malate + succinate + CO_2 + GTP. 2) Cortical washed homogenates from non-ischemic kidneys produced 14.6 ± 1.8 μmoles CO_2/100 mg dry wt hr (M ± SE); cortical homogenates of ischemic kidneys yielded 6.0 ± 3.0 μmoles of CO_2 ($P<0.05$). Similar studies done on slices revealed no such difference between ischemic and non-ischemic kidneys. 3) The activity of α-KG-dehydrogenase was the same in washed cortical homogenates of both ischemic and non-ischemic kidneys. In contrast, malic-dehydrogenase activity was significantly lower in cortical homogenates of ischemic kidneys. 4) Thus, cortical blanching is associated with a specific change in cortical mitochondrial enzymic activity so that both cortex and medullary homogenates have decreased capacities for complete oxidation of substrates. This specific difference in the enzymic activity of mitochondria from the ischemic cortex may explain, in part, the low activity of the above reaction in ischemic cortical homogenates and may be one of the initial metabolic changes which occurs in the ischemic kidney.

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Lipid Composition of the Carcass of Mice Bearing the Krebs-2 Carcinoma.* (32248)

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The profound alterations in the lipid composition of rats bearing transplantable tumors such as the Walker carcinoma 256 have been well known for some time(1-3). These lipid changes are characterized chiefly by a loss of host lipid as the tumor grows and this loss of lipid is mainly in the neutral lipid fraction. Also a high degree of lipemia results as a consequence of the host lipid decrease. These lipid alterations commence when the tumor reaches a size roughly about

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