DISCUSSION

The experiments reported herein have been concerned with elucidating the role of local hypothermia on reduction of renal damages during renal aretry and vein occlusion for one hour as well as the acute compensatory adaptation of the right kidney during occlusion of renal artery and vein of the left kidney.

In renal hypothermic group, the intrarenal temperatures are shown in similar pattern to the results obtained by Schloerb and his associates (1959). Evaluation of the hypothermia on increasing the tolerance of the kidney to ischemia is established by comparing the results of the renal hypothermic group with those of renal normothermic group. In renal normothermic group, RPF, RBF, GFR and urine flow rate of the experimental kidney were shown approximately only one-fifth of the control values. The depression of RPF, as well as RBF, might be due to the post-ischemic obstruction to the renal microcirculation (Diethelm, 1969; Sheehan and Davis, 1959). It has been observed that the stagnant blood in the kidney causes renal damages (Manax, et al. 1964). The hypoxic blood poorly buffers and tends to hemolyse and produces hemoglobin casts on revascularization. Rheinlander and Wallace (1962) found that intracellular pH fell with accumulation of lactic acid during ischemic state. Lysosomes contain a variety of hydrolytic enzymes which are active in the acid pH range and are therefore activated by the tissue acidosis. The releasing of lysosomal enzymes leads to invasion of the injury from cell to cell.

It has been observed that there are vasoconstriction of the fine capillaries, cell aggregation and thrombosis which cause further renal damages (Semb, et al. 1960; Hardaway, et al. 1961; Hinshaw, et al. 1963).

The GFR and urine flow rate after release the occlusion are shown in the similar pattern as RPF and RBF. It is clearly demonstrated that GFR and urine flow rate decrease secondarily to the decreases of RPF and RBF. Low or subnormal glomerular function might be explained on the basis of renal ischemia causing prolonged vasoconstriction of renal arterioles (Selkurt, 1945). However, the decrease of glomerular function after ischemia, as evidenced by low inulin clearance values and low urine output, could not necessarily imply permanent impairment of renal function. It has also been shown that kidneys with subnormal function are not accompanied by serious permanent impairment of either renal viability or capacity to support life as borne out by the results of perfusion-reimplantation experiments (Machioro, et al. 1963). The kidneys returned to their normal function and supported life (Porch, et al. 1960), despite the long lasting depressed functions (Selkurt, 1945; Verney and Vogt, 1943).

By comparison the renal function with the renal normothermic group, the kidneys of renal hypothermic group showed the significantly higher functional status. Renal functions as reflected by RPF, RBF and GFR slightly varied but relatively constant at approximately 60 per cent of the preocclusive values. These functions were not shown complete recovery throughout the experiment. This was suggested to be

the results of cooling (Mitchell and Woodruff, 1957; Semb, et al. 1960; Dottori, et al. 1962). However, it does not seem to re-establish to resting levels which may be due to peripheral vasoconstriction in response to cooling or an alteration in the physical properties of blood. Semb and his associates (1960) observed that the renal peripheral resistance increased during cooling. Mitchell and Woodruff (1957) observed diminishing of the renal cortex circulation after hypothermic ischemia as comparison with those in normothermic ischemia group. They suggested that either there was some accumulation of vasodilating metabolites or persistent vasospasm in the cortical vessels as a result of cooling.

In contrast to RPF, RBF and GFR, urine flow rate of the kidneys in renal hypothermic group was not significantly different from the pre-occlusive value ($P > 0.05$). Some degrees of tubular damages with inability to reabsorb water might be attributed to the observed results. Therefore, it was expected that glomerular function of renall hypothermic group still remained unchanged. These results demonstrated the protective effect of cooling because in addition to the tubular damage. The glomerular damage of renal normothermic group was expected to occur. Schloerb and his associates (1959) also found the transient diuresis in their animals with ischemic cooling for 4 to 8 hours. Wilson (1963) observed a large volume of dilute urine with a high sodium concentration from the previously cooled kidney in one case.

The results of the present studies seem to indicate that the decrease of renal temperatures render the protection of the kidney

from ischemia. The major effect of cooling may be due to decreased metabolic activity and energy utilization of the kidney. It is well known that the basic principle of storage living cells is to arrest the processes of aging and degeneration. Cooling causes a slowing down of the biochemical processes involving in respiration, metabolism, and all the other interactions between the cytoplasm of the cells and their environments. The exponential relationship between renal oxygen consumption and temperature was illustrated by several groups of investigators (Fuhrman and Field, 1943; Fuhrman, et al. 1950; Levy, 1959; Semb, et al. 1960; Harper, et al. 1961). According to the studies of Semb and his associates (1960), the general oxygen metabolism of a dog kidney could be reduced one-half by cooling to 29 ^{o}C or reduced two-third at a temperature of 22 ^{o}C. This was supported by Fuhrman and Field (1943) who obtained exactly the same results. They observed the oxygen consumption at subnormal temperatures in kidney tissue of rats. The reduction in oxygen uptake afforded by cooling was shown to be due to a reduction in tissue oxygen consumption and not due to a deficiency in the amount of oxygen supplied to the kidney tissues causing by ischemic state (Harper, et al. 1961).

One of the protective effect of hypothermia on experimental renal ischemia is to preserve the enzyme content of the nephrons. According to Duguid, et al. (1958-9), succinic dehydrogenase system and non-specific alkaline phosphatase were chosen for the study because of their high concentrations in the nephrons. The disappearance of the former indicates necrobiotic changes while reduction of alka-

line phosphatase activity appears to parallel mitochondrial changes. From their studies, it was observed that hypothermia greatly delayed the onset of ischemic lesion. In the kidneys which were cooled and their pedicles were clamped for 2 hours, the majority of the tubules showed no significant morphological degeneration and diminution of the enzyme contents.

Even though the histological examination of the experimental kidney has not been widely investigated, the protective effect of hypothermia modifying or diminishing the renal damage is expected. Rama Raju and his co-workers (1969) demonstrated that the degenerative changes of the kidney in normothermic groups were moderate to marked and the most of the nephrons of renal parenchyma were involved. The changes were mainly observed in the proximal tubules which showed eosinophilic granular degeneration of the epithelium and calcification. The slight changes of a similar nature were also seen in the distal convoluted tubules. The walls of the vessels thickened and glomeruli congested. Extent of changes varied with duration of renal ischemia. In contrast to the normothermic groups, the changes of the kidney in hypothermic groups were minimal and confined to the proximal tubules only. No microscopic degenerative changes were observed in the glomeruli after one-hour renal ischemia. The capillary congestion and capsular thickening were present in the glomeruli of few animals after 2 and 3 hours of renal hypothermic ischemia. Therefore, as to be expected, the observed results of the present study seem to be in agreement with their studies.

Concerning with the acute compensatory adaptation of the remained kidney after unilateral nephrectomy, Welsh (1944) stated that "After the loss of an active kidney, the functional changes are probably as follows: The tubular excretory mass must at once be cut in half as a result of the anatomical removal of half of the renal tissue of the body. The glomerular filtration rate and effective renal blood flow are, momentarily at least, reduced to a similar extent. Very soon, however, as a result of functional changes, the glomerular filtration rate and effective renal blood flow increase considerably".

The exclusion of one kidney by occlusion of its artery and vein in one of six animals was accompanied by a 15 - 20 mm.Hg rising in mean arterial blood pressure. The similar response was previously observed by Coe, et al. (1968) and Krohn, et al. (1970). This might be due to the increase of distal aortic blood flow while the peripheral resistance remained constant (Krohn, et al. 1970). The other animals in the present study did not show any increase of the mean arterial blood pressure. The controversial results might be explained by decreasing of distal peripheral resistance during an increase of distal aortic blood flow. Therefore, the observed mean arterial blood pressure of the other five animals remained relatively constant.

The unexpected results in the compensatory response of the remained kidney are the decreases of RPF and RBF ($P < 0.05$). This might be probably due to production of arteriolar spasm by stimulation of the autonomic nerve supply to the kidney. The effect of perirenal trauma on the circulation in the outer cortex of the same and opposite kidney

was shown by Hardaway and his co-workers (1961). In the present study, the clamping of renal artery and vein of the left kidney may cause a spasm of the arterioles with diminution of blood flow through the capillary beds of the right kidney.

The GFR of the right kidney during occlusion of left renal artery and vein was shown remained relatively constant ($P > 0.05$). It was approximately between 90 and 103 per cent of the pre-occlusive value. The relatively constant GFR might probably be attributed to the autoregulation of the kidney. Shipley and Study (1951) reported that RBF tended to vary more than GFR and the observed RBF in the present study may not affect on the GFR. The no-response phenomenon of GFR of the present study was in agreement with those obtained in rabbits and dogs by Fajers (1957) and Perlmutt (1967), respectively.

The plasma urea nitrogen during the occlusion shows that the functional elimination of one kidney lead to waste products or metabolites retention in the organism. However, the values obtained at any periods were remained in normal range and were not significantly different from control value ($P > 0.05$). The clearances of urea nitrogen were shown all averaged unchanged ($P > 0.05$). The filtration rate, excretory rate as well as reabsorption rate of urea nitrogen were inconsiderably varied from the controls ($P > 0.05$). It can be noted that the reabsorption rate of urea nitrogen varied in a similar pattern as its filtration rate. This is actually true because of the relative constancy of its excretory rate.

The increased plasma concentrations of potassium seem to

be observed during the occlusion period. Especially, it was significantly increased from the control at the end of the experiment($P<0.05$). The result might probably be explained with the same reason as the increased plasma urea nitrogen. After the function of one kidney is removed, metabolites of cellular metabolism that are usually excreted by a pair of kidneys tend to be retented in the body. It may be suggested that, in the present study, the capacity of the one functioning kidney to excrete potassium do not alter during the 2-hour occlusion period which indicated by the unchange of clearance of potassium. The filtration rates of potassium were shown inconsiderably varied from the control ($P > 0.05$). The variation or fluctuation of the potassium filtration rates may be due to the technical errors in measurement. The potassium excretory rate was shown in a similar pattern as the clearance value. It seemed to increase gradually and was approximately 9 per cent above the control at the end of the experiment. However, it was not considerably different from the control ($P > 0.05$). This finding is in agreement with that of Perlmutt (1967) but contradict to those of Peters (1963) and Rhoads, et al. (1934). The different techniques of the studies may be encountered in comparison the different results. Peters (1963) studied the compensatory response of renal function in uninephrectomized rats while anesthetized dogs were used in the present experiments. Although the dogs were used in the experiments performed by Rhoads and his associates (1934), the technical complications of explanting one kidney and removal the other one made the comparison uncomparable. The potassium reabsorption rates during the occlusion were shown relatively constant ($P > 0.05$). The fluctuation of these values

were demonstrated corresponding to its filtration rates.

In consideration of the plasma osmolality, it was expected that during the occlusion period homeostasis is maintained. The plasma urea nitrogen and plasma potassium tended to increase above the control, but the plasma osmolality was relatively constant ($P > 0.05$). One possibility may be probably explained, that is, some water retention may occur in the same degree as solutes retention. The osmolal clearance as well as negative water clearance were shown relatively constant throughout the experiment ($P > 0.05$). This is in contradictory to the studies of Steels and Borghgraef (1972) who found an increased osmolal clearance during renal compensatory growth in rabbits. They concluded that an increment of osmolal clearance was accompanied by an increase in sodium reabsorption and potassium excretion during 4 weeks after unilateral nephrectomy. In the present experiment, potassium excretion was relatively constant. The difference of the results may be attributed to the difference in the time of studies.

The constancies of water as well as solutes excretion are observed by using negative water clearance, total solid excretory rate and urine flow rate. During the occlusion, negative water clearance was not significantly different from the control value ($P > 0.05$). The total solid excretory rate seemed to increase despite of showing decreased from control at the early period of occlusion. This may be due to the insignificant variation of renal function caused by operation and traumatization. Urine flow rate was also relatively constant during the occlusion ($P > 0.05$). This may be due secondarily to the un-

changed GFR. Evidently, urine output was shown varying in a similar response as the other functions, e.g., urea nitrogen clearance, potassium clearance, osmolal clearance and total solid excretory rate. These functions are slightly improved but do not show any significant difference from their controls.

The non-diuresis response of the kidney was in accordance with the study of Katz (1970) which showed that no sign of compensatory adaptation of rat kidney was observed in 3 hours following unilateral nephrectomy. However, he expected that anesthesia, surgery, volume of infused isotonic saline and dehydration influenced on his experiments. By contrast, the diuretic response was reported despite of the absence of other functional response (Fajers, 1957; Perlmutt, 1967). Fajers (1957) proposed that humoral substances from the occluded kidney were released and carried by the preserved circulation in the capsular vessels of the kidney and transported to general circulation. Finally, these substances directly or indirectly affected on tubular cells and lead to the decreased tubular reabsorption of water in the contralateral normal kidney. Perlmutt (1967) suggested that the diuretic response was probably due to the gradual additional increase in fluid volume by the amount equivalent to the pre-existing urine flow rate from the occluded kidney. The fluid volume expansion was caused by a decrease of the antidiuretic hormone (ADH) activity on tubular cells. After ADH was given intravenously to the experimental animals for two and a half hours during renal artery occlusion, the compensatory actions were prevented including urine output (Perlmutt, 1967). Therefore, the non-

diuresis response of the present experiment may suggest that there is no alteration of ADH-activity during the occlusion.

One parameter of renal function that has never been determined regarding to the compensatory response after exclusion of one kidney is the urine acidification. In the present study, urine pH was shown to decrease significantly from the control value even at the early period of the occlusion ($P < 0.05$). This might probably be attributed to the increase of tubular activity to secrete hydrogen ions. The effect of mannitol diuresis on acid excretion (Steinmetz and Bank, 1963) can not be expected to occur because urine flow rate has been induced by mannitol since the control period. However, several tubular factors may play a role on the observed increase of urine acidity. The sodium-hydrogen ions exchange mechanism may be accelerated with increased delivery of sodium to the remaining nephrons. In the present study, it may be expected that hydrogen tubular secretion is increased corresponding with the increase of sodium reabsorption.

According to Pitts and Alexander (1945), the secretion of hydrogen ions is linked to the synthesis of carbonic acid molecules from carbon dioxide and water. This reaction is under the influence of enzyme carbonic anhydrase (CA). The carbonic acid, then, dissociates and liberates a hydrogen ion for exchange with sodium ion in the tubular lumen. The increased urine acidity observed in the present experiment might be attributed to the increased CA activity because of the acid load on the remained kidney after functional elimination of one kidney.