LITERATURE REVIEW

Application of the general principle of hypothermia for conservation of ischemic organs is of recent origin. The concept of hypothermia states that at reduced temperature there is a decrease in tissue metabolism resulting in a decreased requirement of oxygen by the ischemic tissues. This inturn may prevent or modify some damages which are observed after ischemia is produced at normal body temperature.

The effect of renal hypothermia has been extensively studied. Markland and Parsons (1963) classified the histological ischemic renal damages into 5 grades. In grade 1, the renal cortex appeared to be normal and any evidence of tubular degeneration was revealed only by special staining and was probably of little significance. Epithelial cloudy swelling was apperent in the sections which were stained with hematoxylin and eosin, classified as grade 2. A few casts were present and insignificant epithelial-cell calcification was observed. In grade 3, any evidence of cortical necrosis still could not be shown but there were definite tubular necrotic changes. The more severe reactions to renal ischemia stated above were classified as grade 4. There were a few areas of cortical necrosis along with widespread tubular necrosis. The greater bulk of renal cortex might be viable. In grade 5, the bulk of the necrotic cortex was clearly observed. They further found that recovery of renal function subjected to ischemia was possible in grade 1 to 3, less possible in grade 4 and

highly improbable in grade 5. Oliver, et al. (1951) and Rama Raju, et al. (1969) demonstrated that the cells of proximal tubules were the most susceptible to ischemia while the glomeruli and intrarenal vasculature appeared to be relatively immune. Changes in physiological function after varying periods of renal ischemia have also been widely studied and the most important contributions were those of Selkurt (1945) and Porch, et al. (1960). They concluded that the effect of circulatory arrest on renal function was directly related to its duration. An approximately time-scale can be constructed to indicate the degree of renal function depression. The temporary or permanent damages might be expected following the specific period of renal ischemia.

Several investigators demonstrated the value of hypothermia in preventing or modifying all of the ischemic renal damage (Bogardus and Schlosser, 1956; Schloerb, et al. 1957; Mitchell and Woodruff, 1957; Stueber, et al. 1958; Duguid, et al. 1958-9; Mitchell, 1959; Birkeland, et al. 1959; Kerr, et al. 1960). Thus, increasing the tolerance of the kidney to ischemia was observed. Numerous studies were performed on the effect of cooling on renal ischemia and 3 principal methods were involved. First, perfusion cooling technique, the renal substance was cooled by infusion of a hypothermic perfusate into the renal artery (Markland and Parsons, 1963; Dottori, et al. 1962; Matloff and Gowen, 1962). Second, external parenchymal cooling or simple surface cooling technique, the renal temperature was reduced by applying a cooling source directly to the renal parenchyma (Bogardus and Schlosser, 1956; Schloerb, et al. 1957; Mitchell and Woodruff, 1957;

Stueber, et al. 1958; Birkeland, et al. 1959; Wilson, 1963; Metzner and Boyce, 1972). The third technique, whole body or generalized hypothermia, the renal temperature was lowered secondarily to the reduction of the whole body temperature (Moyer, et al. 1957).

There has been widely discussed about the best technique for producing short-term preservation by hypothermia. In general, some forms of external parenchymal cooling appeared to be the method of choice. Wilson (1963) reported that the application of sterile ice to the surface of the kidney during the period of renal ischemia could be satisfactorily performed. He used this technique with 22 patients. The more recent studies of Metzner and Boyce (1972) have been shown that slush cooling seemed to offer a simple technique for regional renal hypothermia. Several investigators preferred the external parenchymal cooling technique to any other techniques. These preferences were comparable to the studies of Matloff and Gowen (1962). They concluded that the protective effect rendered by hypothermic perfusion was due primarily to the low renal temperature and normal perfusion had neither a beneficial nor a deleterious effect on the ischemic kidney. This conclusion was confirmed by Martin and his associates (1970). They preserved the functions of the kidney which were maintained extracorporeally for 8 hours by using 2 techniques. First, surface cooling technique at 5 ^{o}C and second, perfusion technique using cooled plasma and a variety of electrolyte solution. The results suggested that hypothermia alone was the best method for preserving renal function. However, the danger of cortical necrosis

was reported following the use of simple surface cooling technique (Semb, 1956; Mitchell and Woodruff, 1957; Mitchell, 1959; Kerr, et al. 1960). According to the studies of Kerr and his associates (1960), they found that simple surface cooling technique using direct application of ice cubes was dangerous. The areas of renal cortex in contact with ice cubes were shown blanched and firm. Although microscopic studies were not carried out, it was expected that cortical damage resulting from such technique.

Local renal hypothermia was begun in 1956 after consideration of the experimental work and clinical experience of Carl Semb in Norway. He recorded the clinical results of renal pedicle occlusion during partial resection of 15 solitary kidneys out of 226 resections. He occluded the renal pedicle for one and a half hours without evidence of permanent renal damage. He concluded that 10 minutes of occlusion produced little functional depression, 20 to 25 minutes produced moderate functional depression, while 40 minutes of occlusion produced severe functional depression which usually subsided in 2 to 4 weeks. With local cooling, the studies of Birkeland and his associates (1959) and Mitchell (1959) were shown that ranal function was only temporarily depressed and parenchymal damage was insignificant after shutting off renal circulation for 2 hours. In accordance with the studies of Birkeland and his associates (1959), renal temperature of 5 to 17 ^{o}C conferred more protection than total body hypothermia of 28 to 30 ^{o}C.

Lower renal temperature appears to afford a higher degree

of protection. The experimental results in animals have been extensively observed. However, it is difficult to obtain the ideal temperature range which the ischemic kidneys should be cooled to achieve maximum functional preservation. Bogardus and Schlósser (1956) demonstrated that bilateral local chilling of the canine kidneys to a temperature of 20 to 25 °C during a 2-hour period of renal peddicle occlusion resulted in a less marked rise of serum creatinine than in those undergoing the same period of occlusion under normothermic conditions. The protective effect of local renal hypothermia at 20 °C was also observed by Rama Raju, et al. (1969). They performed renal hypothermia during 1 to 3-hour periods of renal ischemia in dogs using renal pelvis irrigation technique. They found distinct mild to severe degenerative changes in the renal parenchyma in all the normothermic groups. The regenerative activity was observed in animals sacrified after 3 weeks of post-operation. In hypothermic groups, renal ischemia was carried out at approximately 20 °C. The degenerative changes were minimal when compared with the normothermic groups. The regenerative activity was much more marked and the mortality rate was also significantly lower in these hypothermic groups.

Stueber and his associates (1958) noted that 10 uninephrectomized dogs survived 6 hours of renal pedicle occlusion at 0 to 5 °C while another 10 uninephrectomized dogs all succumbed following the same period of normothermic occlusions. In 1957, Schloerb and his co-workers locally cooled the remaining kidney in uninephrectomized dogs between 2 and 4 °C. Ten dogs cooled for 8 hours with com-

plete pedicle occlusion survived. They were shown a transient elevation of serum creatinine which returned to normal within 24 hours. Kerr and his associates (1960) aimed at a renal temperature of 25 to 30 °C to be attained in 5 to 10 minutes when they performed local renal hypothermia. Wilson (1963) felt that a renal temperature of 18 to 22 °C attained in 15 minutes was more desirable than that of Kerr and his associates (1960). Wickham and his co-workers (1967) demonstrated that 84 minutes of renal ischemia at 20 °C failed to produce any permanent depression of renal function. Their works were based on the experiments performed by Bickford and Winton (1937) who suggested that renal temperature of 20 °C should be aimed during performing renal hypothermia.

In 1963, Newman performed partial renal hypothermia during clamping of a definite branch of renal artery in dogs. He used ice during the process of melting as a surface cooling agent. After 30 minutes the ice and arterial clamp were removed, the kidneys were replaced and the wound closed. The animals were permitted to survive varying periods of time before the kidneys were removed and examined histologically. He found that the microscopic sections showed varying degrees of perirenal and capsular fibrosis and such fibrosis was found not relating to contact with ice. He concluded that melting or 0 °C ice was an effective cooling agent. This conclusion was in contradictory to those of Kerr, et al. (1960) and Mitchell and Woodruff (1957). According to the studies of Mitchell and Woodruff (1957), temperatures below 10 °C in sheep's kidneys produced solidification of renal cortex.

This resulted in peripheral renal infarcts with fatty necrosis and subsequent fibrosis.

It has been well recognized that man can live normally with one kidney. The fact that a kidney enlarges following one of a pair of organs is destroyed by diseases or operation has been accepted. Compensatory processes are among the most important of the adaptive mechanism. The information on the chemical and morphological changes which follow reduction of renal mass or unilateral nephrectomy has been accumulated. However, the mechanisms that initiate and sustain compensatory renal responses remain obscure. Several possible causes have been extensively investigated including the increased work load (Allen and Mann, 1935; Bollman and Mann, 1935), humoral factors (Goss, 1963; Braun-Menendez, 1958; Lowenstein and Stern, 1963; Lytton, et al. 1969) and vascular alterations (Krohn, et al. 1970).

The concept of increased renal work underlies the phenomenon of compensatory renal response was derived largely from studies showing accelerated kidney growth of both intact and uninephrectomized animals fed with diets rich in protein and urea (Allen and Mann, 1935). Proponents of the work hypertrophy theory attributed compensatory kidney growth to the increased excretory loads of urea and other solutes placed on the reduced renal mass, and made the assumption that the size of the kidney was determined by the amount of substance which should be excreted. Allen and Mann (1935) showed

that in rats or rabbits which were fed with a diet containing 20 per cent urea, the kidneys developed much larger than the control animals on the standard diets. However, the role of an increase in renal work has not been clearly established. Many investigators demonstrated that solute load or work load did not appear to be primarily responsible for the renal enlargement (Rhoads, et al. 1934; Halliburton and Thomson, 1967; Katz and Epstein, 1967; Kiil and Bugge-Asperheim, 1968; Kaufman, et al. 1974). Katz and Epstein (1967) performed unilateral nephrectomy in rats. They found that during the first 24 hours, the remaining kidney increased in size before there was any increase in GFR. After 3 days, the rise in filtration rate outstripped the increase in weight. They concluded that an increased reabsorptive work load per gram of kidney tissue was not the initial stimulus for the early changes of compensatory renal hypertrophy. Large infusions of urea and saline were given to rats by Kauker, et al. (1970). These increases of the load of urea and solutes were sufficient to produce significant elevations of blood urea nitrogen, but failed to produce any increase of GFR.

Concerning the vascular alteration concept, it has been suggested that the functional and anatomical enlargement of the remaining kidney after ablation of one kidney was caused by an immediate increase in its blood flow. The early renal vascular changes resulting from unilateral nephrectomy were studied in dogs by Krohn and his associates (1970). Almost immediately after the operation, a mean increase in RBF of 27 to 33 per cent of the un-operated kid-

neys was shown. However, this vascular alteration concept was not supported by the results of ureteroperitoneostomy performed by Bugge-Asperheim and Kiil (1968). They diversed the urine from one kidney into the peritoneal cavity in dogs. This resulted in an increase in GFR in the intact kidney which was equal to that seen after nephrectomy.

While the reasons for compensatory response of the intact kidney after functional exclusion of one kidney are not entirely clear, there is strong evidence suggesting that changes in humoral substances controlling renal hyperplasia are involved. Lytton (1974) reported that there were 4 major groups of experiments in which the humoral factors were suggested to involve the compensatory renal response after unilateral nephrectomy. The experiments involved as follows: a) the renal macerates and extracts (Chopra and Simnett, 1969; Goss, 1963; Williams, 1962), b) the post-nephrectomy serum (Ogawa and Nowinski, 1958; Lowenstein and Stern, 1963; Preuss, et al. 1970), c) the parabiotic experiments (Braun-Menendez, 1958; Lytton, et al. 1969), and d) the cross-circulation experiments (Vroonhoven, et al. 1972). However, the studies performed by Thompson and Lytton (1967) was shown that the humoral substances might not be responsible for the compensatory renal enlargement. They found no increase in the weight of the kidneys of the parabiotic rats. They suggested that there was probably not a diffusible humoral substances liberated after nephrectomy.

The rate and degree of compensatory renal response have been extensively studied which were appeared in several reviews (Malt, 1969; Marshall, 1963; Williams, 1962; Lytton, 1974). The initial weight gain of the residual kidney was detected immediately after recovery from the shock of operation and then graduälly increased in mass (Rollason, 1949). Karsner, et al. (1934) demonstrated a 75 per cent restoration of renal mass in the rats 48 hours after contralateral nephrectomy. A 100 per cent increase in tritiated-thymidine uptake by tubular cells indicating a 100 per cent increase in the rate of tubular cells proliferation was also observed. Rhoads, et al. (1934) found an eleven-fold increase in proximal tubular mitotic rate in rats 40 hours after contralateral nephrectomy. Several factors have been shown to influence the rate and degree of the compensatory response. The effect of age on the compensatory response of growth and function after unilateral nephrectomy was studied in weanling and young adult rats (Galla, et al. 1974). The data indicated that the magnitude of compensatory growth in the immature animals was greater than in adults. Jackson and Shiels (1928) and Arataki (1926) showed that the amount of compensatory renal hypertrophy was much greater when the nephrectomy was performed in young rats than in adolescent or mature animals. In addition, Moore (1929) found that unilateral nephrectomy in white rats during the period of active nephrogenesis had no effect on the total number of glomeruli in the opposite kidney. In man, an inverse relationship between function and age at the time of nephrectomy (Hogeman, 1948), or at the time of study after nephrectomy (Kohler,

1944) has been demonstrated implying a diminished functional response to uninephrectomy in older patients.

It has been shown that the compensatory renal hypertrophy could be modified by endocrines. The compensatory response was inhibited by hypophysectomy (Ross and Goldman, 1970). Testosterone has been shown to enhance the compensatory renal growth in mice (Pfeiffer and Gardner, 1940). Physical and physiological factors affecting the compensatory renal response were studied. In rats and rabbits which were placed on forced exercise the kidneys did not showed more hypertrophy than the control after nephrectomy (Allen and Mann, 1935). In the same investigation, the animals which were permitted to undergo gestation several times did not have larger kidneys than the control.

Many investigators agreed that the increased mass of the remaining kidney was due to both cellular hypertrophy and hyperplasia. The cellular hypertrophy occurred earlier and was quantitatively more important than cellular hyperplasia (Arataki, 1926; Rollason, 1949; Halliburton and Thomson, 1965; Johnson and Roman, 1966). Evidence of renal hypertrophy could be found as a few hours (Johnson and Roman, 1966; Rollason, 1949) while cell division started only after 18 hours and reached its peak at 48 hours after contralateral nephrectomy (Johnson and Roman, 1966; Rollason, 1949; Williams, 1961). Approximately 75 per cent of the final increase in renal weight was due to cellular hypertrophy and the remainder to cellular hyperplasia (Johnson and Roman, 1966).

Functional responses of the remaining kidney to nephrectomy have been variably studied. Van Slyke and his associates (1934) stated that removal of one kidney was followed by an increase in the blood flow, oxygen consumption and urea clearance of the remaining kidney. They demonstrated that the increase in the most cases appeared to reach its maximum within a month. The average increase of renal blood flow was 68 per cent, oxygen consumption 81 per cent, and urea clearance 43 per cent of the pre-operative values. Studies by Bugge-Asperheim and Kiil (1968) indicated that GFR and tubular sodium reabsorption increased 5 to 30 days after either unilateral nephrectomy or ureteroperitoneostomy. Rous and Wakim (1967) showed a 20 per cent increase in creatinine clearance and a 30 per cent increase in PAH clearance of the remaining kidney within 24 hours after nephrectomy in dogs. These results were compared to several investigations which an increase of 20 to 50 per cent in GFR and RPF of the remaing kidney have been reported (Rhoads, et al. 1934; Donadio, et al. 1967). Furthermore, renal blood flow might equal and even surpass that of both kidneys before nephrectomy (Levy and Blalock, 1938).

The timing of the compensatory response of the remaing kidney after contralateral nephrectomy varies among different species. In the rat, Potter and his co-workers (1969) noted a mean increase approximately 10 per cent of GFR and tubular reabsorption of sodium in the first two and a half hours after nephrectomy. They suggested that this early change was the initiating event of compensatory renal hypertrophy. By contrast, Peters (1963) found no change in GFR of the kidney

within the first 18 hours after removal of its partner. Katz and Epstein (1967) found an early and significant increase of renal mass 24 hours after nephrectomy. This finding was in agreement with those of Rollason (1949) and Johnson and Roman (1966). In anither study of the rat, renal mass reached 65 per cent of the pre-nephrectomy value 5 days after operation and 90 per cent at 40 days (Addis and Lew, 1940). In dog, the significant increases of GFR and RBF were demonstrated / 24 hours after contralateral nephrectomy and the compensatory increases were complete within the first few post-operative days (Rous and Wakim, 1967). In the rabbit, no signs of compensatory response of the residual kidney were detected within 2 hours after nephrectomy (Fajers, 1957). There has been little previous studies concerning the rate of increase in function of the remaining kidney in man. Ogden (1967) studied renal function before and after nephrectomy in 29 healthy adults. The post-operative studies were performed 1 to 18 days, with an average of 7.1 days. He found an extremely rapid 40 per cent increase in the clearances of creatinine and PAH by the remaining kidney. Therefore, in man, the compensatory renal response seemed to occur as soon as 24 hours after nephrectomy.