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Uranyl Nitrate Induced Polyuric Acute Tubular Necrosis in Rats

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We investigated the pathobiological course of uranyl nitrate (UN) induced polyuric acute tubular necrosis (ATN) in male Sprague Dawley rats. UN (5mg/kg, 15mg/kg and 30mg/kg) in 5% $NaHCO_3$ induced weight loss, polydipsia, and polyuria 24 hrs after injection when compared to the controls which were treated with 5% $NaHCO_3$ only. Twenty four hours following the injection of UN, serum creatinine and blood urea nitrogen levels had increased. These changes continued for at least 72 hours, although the concentration of uranium had decreased. Light microscopic studies conducted 24 hours after injection, revealed partial degeneration and necrosis of the proximal tubules and many casts in the distal convoluted tubules. These changes progressed for 72 hours. Despite this tubular damage, the glomeruli were relatively intact. 5 days after injection, the epithelial cells lining the proximal tubules displayed regenerative activities; these findings were more prominent after 10 days. Through electron microscopic examination, we observed the destruction of mitochondria in the proximal tubular cells, a possible cause of polyuria. Ten days post injection regenerative activities in the proximal tubular cells showed that the maturation of intracellular organelles followed the proliferation of the premature cells.

Key Words: Rat Kidney, proximal tubular cells, polyuric ATN.

Acute tubular necrosis (ATN) is the most common pathologic entity responsible for the clinical state of acute renal failure (ARF). The latter term refers to the syndrome associated with acute suppression of renal function, accompanied by severe oliguria but rarely anuria (Robbins *et al.* 1984; Solez 1983).

The causes of ATN may be roughly divided into two main groups; those cases in which there is a direct poisoning of tubules, chiefly the proximal convoluted tubules, by various noxious agents such as heavy metals (Toxic ATN), and those cases that have a preceding episode of renal ischemia often associated with hypotension (Ischemic ATN).

Avasthi *et al.* (1980) reported that oliguric ARF in rats exposed to UN showed a decrease in the number and the area of endothelial fenestrations, and a swelling of podocytes in the glomerulus. This caused the reduction of the glomerular ultrafiltration coefficiennt and oliguria in UN induced ARF.

Autopsy specimens with ATN are very common, but we frequently overlook the early diagnosis of ATN in the human kidney. In this research, the complete course of polyuric ATN, from partial degeneration to frank necrosis without definite changes in the glomeruli to regeneration, was investigated while studying the metabolism of the uranium compound in rats. Following injection of UN into the rats' tail veins, the changes and relationships in body weight, water intake and urine output were observed for 12 days.

MATERIALS AND METHODS

Male Sprague Dawley rats, weighing 170-190g, were fed *ad libitum* a synthetic diet based on NIH-7-open formula (Bieri et al, 1977) and water. 15 rats were housed in individual metabolic cages (Myung Jin Instrument Co., Seoul, Korea). During this period, daily changes in body weight, water intake, and urine output of each rat were measured, and rats without a weight gain were exchanged for healthier ones. The rats were then divided into 4 groups (4 rats/group), and injected with 30mg, 15mg and 5mg of uranyl

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nitrate ($UO_2(NO_3)_2 . 6H_2O$, Art 8476, E. Merck) per ml of 5% $NaHCO_3$ per kg body weight, through the tail veins. A five percent $NaHCO_3$ solution pH 7.4, was injected into 3 rats as the control. All solutions were sterilized using 0.22μ membrane filtres (Millipore Filter Corp. MA. USA).

Individual rat's body weight and water intake were measured daily, and the 24 hr urine was collected separately by means of devices attached to the metabolic cage. The rats were sacrificed periodically, 24 hrs, 72 hrs, 5 days and 12 days after injection. All experiments were repeated 4 times.

Immediately after sacrifice, whole blood was collected through a cardiac puncture using a 21 gauge needle. The large, solid organs (lung, kidney, testes, spleen, liver, stomach, intestine, bone and brain) and their cut surfaces were examined by the naked eye and then preserved for morphological studies.

Serum was stored in the freezer at −70°C, the 24 hr urines were refrigerated at 4°C with a few drops of toluene.

We used a creatinine kit (RM 119-K, Iatron, Lab. Inc., Tokyo, Japan) to measure creatinine in the serum and 24 hr urine. Under alkaline conditions, serum creatinine forms a picric acid-creatinine complex (Jaffe reaction). The color intensity of this complex was measured at 520 nm with a spectro-photometer (DU 8 B Spectrophotometer, Beckman) against a standard creatinine solution (5 mg/dl).

BUN measurements were performed by the urease-indophenol method using a BUN Kit (RM 118S-K, Iatron Lab. Inc., Tokyo, Japan). Ammonia released from urea by urease caused the reaction mixture to turn green in the presence of sodium nitrosoferric cyanide. The absorbance was measured at 600nm with a standard urea nitrogen solution (30mg/dl).

The level of calcium in the serum was also measured by a colorimetric method using the chelating agent *o*-cresolphthalein complexon (RM 117-K Iatron Lab. Inc., Tokyo, Japan) under alkaline conditions at 575 nm.

Serum inorganic phosphate was measured using the *Pi* set (RM 123-K Iatron Lab. Inc., Tokyo, Japan) at 650 nm. In the test for inorganic phosphate, all glassware was soaked in 5% HCl for 2hrs and rinsed with double distilled water to reduce the nonspecific reaction.

For light microscopy, rat kidneys were fixed in 10% neutral formalin (Art 4001, E. Merck W. Germany) for 48 hrs, embedded in parafin, and stained with hematoxyline eosin.

For electron microscopy, organs were prefixed in 2% paraformaldehyde (15812-7, Aldrich Chemical Co., Milwaukee, Wisconsin USA) and 2.5% glutaraldehyde (G 5882, Grade 1, Sigma Chem. Co., St. Louis Mo. USA) for 4 hr and washed in 0.2M phosphate buffered

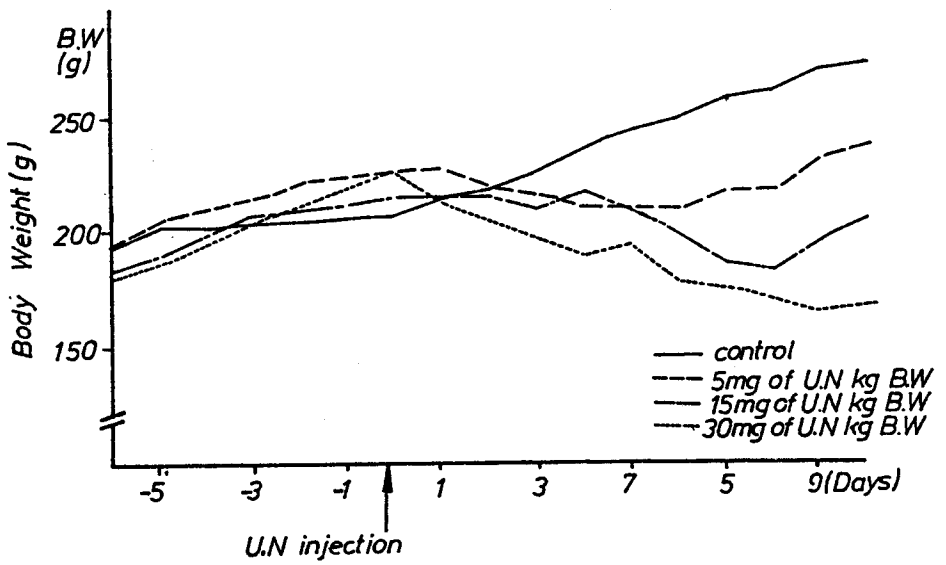

Fig. 1. *Changes in body weight of Sprague Dawley rats injected with uranyl nitrate solution. Male Sprague Dawley rats, weighing 170-190gm, were housed in individual metabolic cages and fed a synthetic diet based on NIH-7-open formula and water. After 7 days, the rats were divided into 4 groups and each group was injected with a specific concentration of UN dissolved in 5% $NaHCO_3$. 5% $NaHCO_3$ was injected to the control rats. Weight changes were measured daily. At 24 hrs, 72 hrs and 10 days, rats from each group were sacrificed and various specimens were collected for further study.*

saline, pH 7.4, for 30-60 minutes. Following a 2 hour fixation in 1% OSO_4 (20103-6, Aldrich Chem. Co., Milwaukee, Wisconsin, USA), dehydration in a series of graded alcohols to 100% ethanol, and embedding in epon 812, ultrathin (500-600Å) sections using a LKB type 3 ultramicrotome were prepared. After staining the sections with uranyl acetate and lead acetate they were observed under the EM (JEOL 100B).

The students' t test, simple linear regression and multiple regression analysis were used to determine the significance of all data using the program "Stat Plus" developed by Apple® Computer.

RESULTS

Prior to uranyl nitrate treatment, each rat gained weight daily in the metabolic cages. Twenty four hours after injection, the rats treated with UN 30mg/kg showed a weight loss which continued for 12 days. On the contrary, the control rats gained weight continuously. The amount of weight loss was dependent on the concentration of UN in the range of 5mg/kg-30mg/kg (Fig. 1).

UN significantly increased water intake and urine output 24 hrs after injection. These findings became more clear by the 3rd day (Table 1). The rats injected with UN 30mg/kg and 15mg/kg developed severe fluctuations in the amount of water intake and urine output, while, the rats with UN 5mg/kg exhibited a

Table 1. Changes in water intake and urine output 24 hours and 72 hours after injection of uranyl nitrate solutions into Sprague Dawley rats

	Treatment of uranyl nitrate	Before injection	24hrs after treatment	72hrs after treatment
Water intake	30mg/kg	36.0±3.4	46.7± 7.6 (P<0.05)*	60.5± 9.0 (P=0.025)
	15mg/kg	34.0±3.4	44.0± 4.6 (P=0.061)	64.0±14.1 (P=0.030)
	5mg/kg	34.0±4.2	36.2±13.8 (P=0.643)	63.5±18.9 (P=0.036)
	0mg/kg	39.3±4.9	41.3± 7.1 (P=0.420)	38.0± 8.0 (P=0.660)
Urine output	30mg/kg	8.4±3.1	30.5± 7.5 (P=0.004)*	43.5± 2.1 (P<0.001)
	15mg/kg	8.0±2.7	25.0± 5.5 (P=0.003)	42.8± 9.6 (P=0.007)
	5mg/kg	7.5±2.0	15.3± 8.6 (P=0.107)	40.3±11.0 (P=0.005)
	0mg/kg	10.0±2.3	9.3± 4.4 (P=0.654)	11.4± 3.4 (P=0.54)

Changes in water intake and urine output for each group of rats were measured daily for 7 days prior to UN injection and for 12 days following injection.

* Numbers in parentheses indicate *P* values between the amounts of before and after U.N. treatment.

All values are means ± S.D.

The other legends are the same as those in Figure 1.

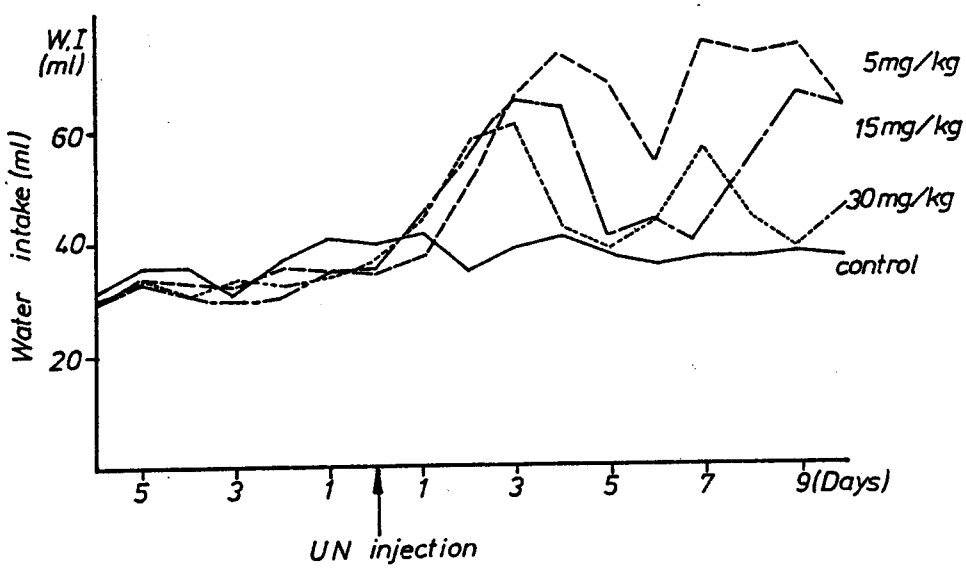

Fig. 2. Water intake in Sprague Dawley rats injected with uranyl nitrate solutions. Legends are the same as in Table 1.

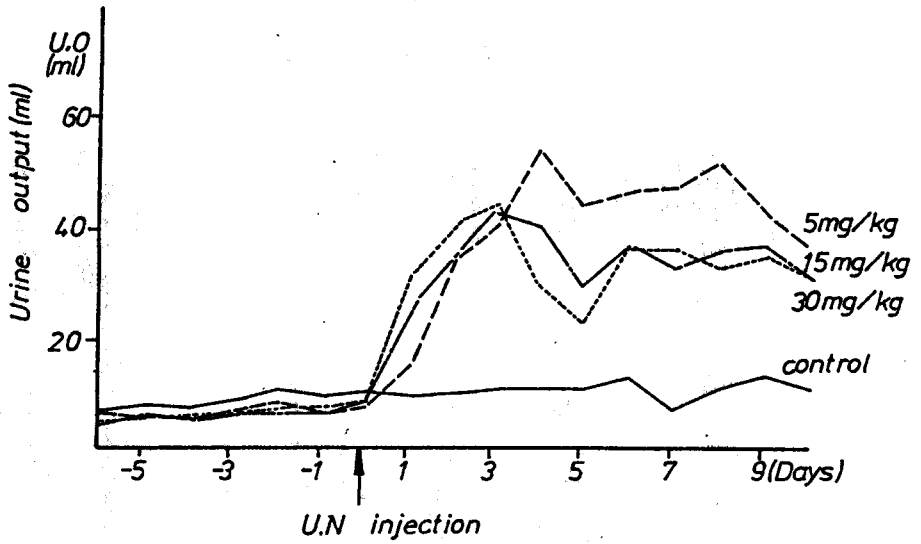

Fig. 3. Urine output in Sprague Dawley rats injected with uranyl nitrate solutions. Legends are the same as in Table 1.

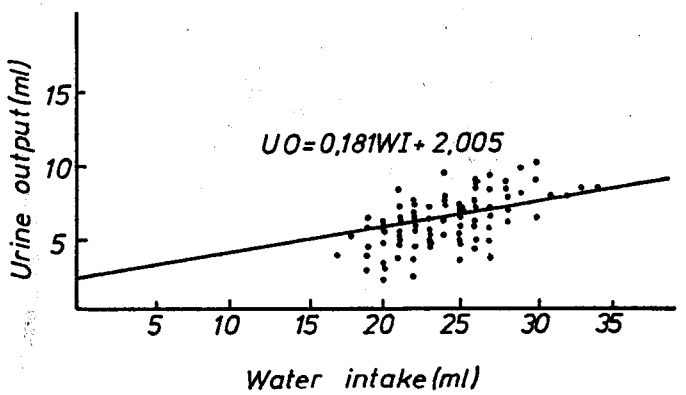

Fig. 4. Simple linear regression and scatter diagram detailing water intake and urine output in Sprague Dawley rats before uranyl nitrate injection.

Table 2. Multiple regression analysis among water intake, body weight and urine output of Sprague Dawley rats intravenously injected with uranyl nitrate solutions

U.N treatment	Multiple regression	P-value
Before	U.O=−3.579+0.107 WI+0.033 BW	P<0.001
30mg/kg	U.O=10.749+0.685 WI−0.050 BW	P<0.001
15mg/kg	U.O=35.939+0.679 WI−0.177 BW	P<0.001
5mg/kg	U.O= 1.963+0.757 WI−0.038 BW	P<0.001

All of the data applied in this analysis were derived from Figures 1,2 and 3.

prolonged increase in the amount of water intake and urine output (Figs. 2 and 3). We noted a significant association between water intake and urine output in male Sprague Dawley rats before UN injection (P<0.001, R=0.785, Fig. 4). Table 2 is a multiple regression analysis of urine output, water intake and body

Table 3. Serum creatinine levels in Sprague Dawley rats treated with uranyl nitrate solution

Treatment of U.N (mg/kg of BW)	Serum creatinine (mg/dl)		
	24hrs after injection	72hrs after injection	>10days after injection
30	2.21±1.23 (P=0.001)*	3.85±0.70 (P<0.001)	1.08±0.18 (P=0.009)
15	0.99±0.19 (P=0.005)	2.19±0.39 (P<0.001)	0.89±0.07 (P=0.09)
5	0.63±0.12 (P>0.1)	1.76±0.34 (P<0.001)	0.78±0.11 (P>0.5)
0‡	0.70±0.20	0.70±0.20	0.70±0.20

The legends are the same as in Figure 1.

* Numbers in parentheses indicate p values between the control and the test group, based on the students' t test.

‡ 5% $NaHCO_3$, solution, pH 7.4, was injected instead of uranyl nitrate solution.

All values are means ± S.D.

Table 4. Blood urea nitrogen in Sprague Dawley rats intravenously injected with uranyl nitrate solutions

Treatment of U.N (mg/kg of BW)	BUN (mg/dl)		
	24hrs after treatment	72hrs after treatment	>10days
30	52.1±28.9 (P<0.001)*	94.0± 5.7 (P<0.001)	32.4±17.2 (P=0.001)
15	32.0± 4.9 (P<0.001)	53.0±29.7 (P<0.001)	26.4±14.0 (P=0.007)
5	22.3± 3.6 (P<0.001)	52.5±16.3 (P<0.001)	14.6± 4.0 (P>0.5)
0‡	14.4± 2.6	14.4± 2.6	14.4± 2.6

Legends are the same as Table 3.

Table 5. Ca^{++} and Pi concentration in serum and creatinine concentration in 24 hr urine in rats following IV injection of UN solutions

After U.N injection (hrs)	Treatment of U.N (mg/kg of BW)	Ca^{++} (mg/dl)	*Pi* (mg/dl)	Creatinine in urine (mg/kg of BW/24hrs)
24	30	9.6±0.6	11.2±2.4	47.3± 5.2
	15	8.9±1.0	10.3±1.1	37.3± 7.6
	5	8.8±0.8	11.8±0.9	40.3± 5.7
	0	10.6±2.3	9.1±2.2	32.3±12.5
72	30	14.7±2.0	7.2±1.1	29.0±11.5
	15	16.5±0.7	7.9±1.5	50.0±27.8
	5	16.8±1.2	8.7±0.3	36.0±22.3
	0	10.6±2.3	9.1±2.2	32.3±12.5
>10days	30	9.1±1.4	6.3±1.4	23.9± 7.6
	15	12.0±3.0	7.8±1.3	29.5± 7.6
	5	13.0±0.4	7.8±2.9	29.4± 7.4
	0	10.6±2.3	9.1±2.2	32.3±12.5
		(8.8–16.7)*	(6-12.2)	(10-46)

* Numbers in parentheses indicate the minimum and the maximum values of Ca^{++}, *Pi* in serum and creatinine in urine, respectively, measured in our laboratory.

All values indicate means ± S.D.

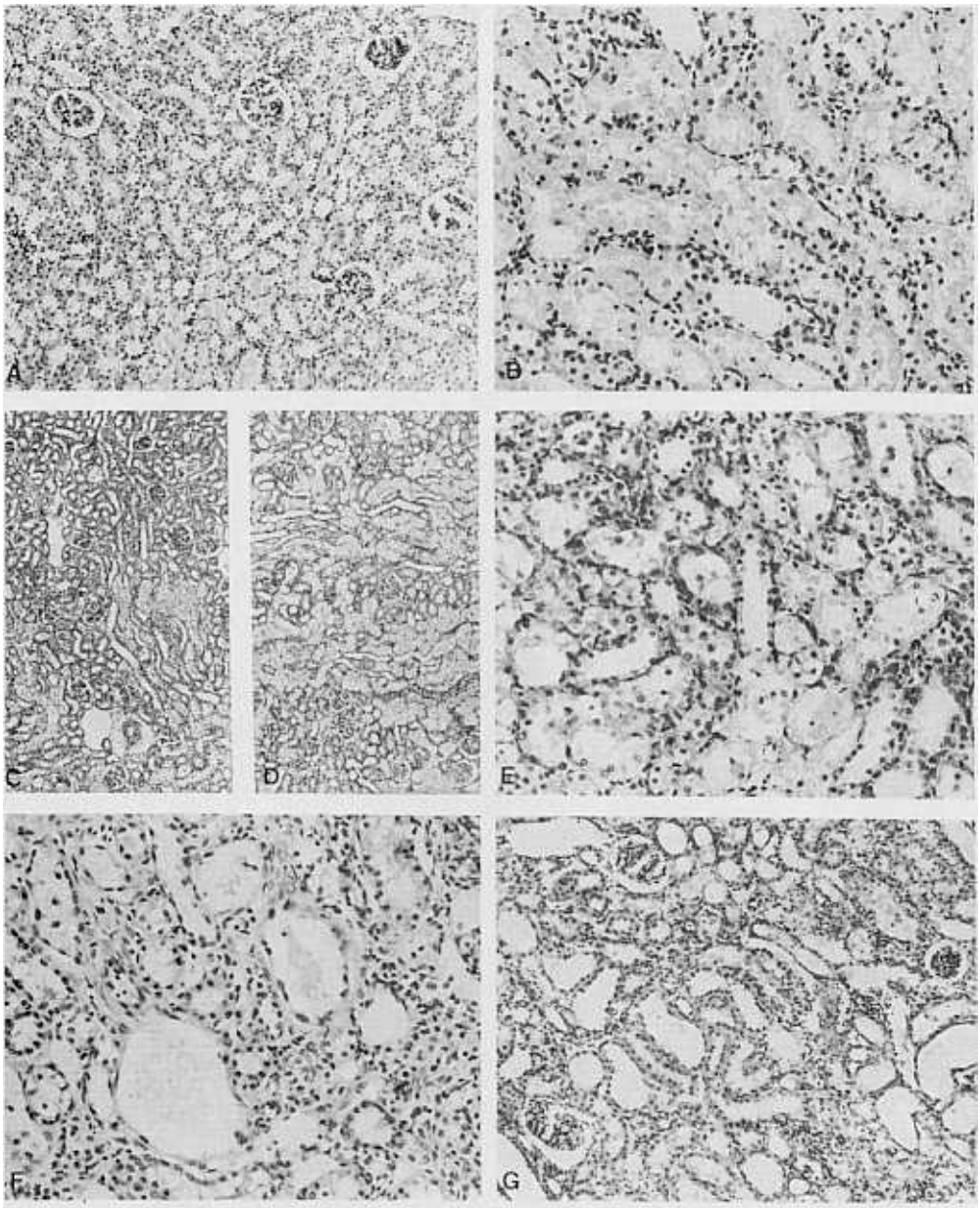

Fig. 5. *Light microscopic findings in the proximal renal tubules in male Sprague Dawley rats after injection of uranyl nitrate (30mg/kg, 15mg/kg, and 5mg/kg of body weight). Note the proximal tubules showing partial degeneration with the admixture of a frank necrotic area after 24 hrs in the 15mg/kg treated rats (A, × 100). Epithelial cells with and without nuclei are seen simultaneously in the same tubule after 24 hrs in the 30mg/kg treated rats (B, × 200). C and D reveal the overall necrosis of the tubules after 72 hrs. Multifocal areas showing complete tubular necrosis are evident even in the low power view (C, 5mg/kg × 40). The degree of distruction increased as the concentration of UN increased (D, 30mg/kg, × 40). In spite of severe tubular damage, the glomeruli are relatively intact, and interstitial infiltration of inflammatory cells was absent. E-G represent the regenerative activities of the proximal tubules. Five days post UN injection, cells with large hyperchromatic nulei were observed (E, 5mg/kg, × 200). After 12 days, small and large dilated tubules lined with irregularly shaped epithelial cells including hob-nail shaped cells (F, 15mg/kg, × 200) were intermixed. In the 30mg/kg treated rats (G, × 100), there is a collection of the interstitial mononuclear cells after 12 days. This is remarkable when compared to the earlier phases.*

Table 6. Light microscopic changes in the renal tubules of Sprague Dawley rats intravenously injected with uranyl nitrate solutions (30mg/kg, 15mg/kg, 5mg/kg of body weight)

After U.N injection	Concentration of U.N injected into the rats(mg/kg of BW)	Proximal tubular necrosis	Casts in distal tubules	Regenerating activities of the tubules	Interstitial inflammatory cell infiltration
24 hrs.	30	++	++	−	−
	15	++	++	−	−
	5	+	+	−	−
72 hrs.	30	+++	++	+	−
	15	+++	+++	−	−
	5	+	+	±	−
5 days	30	±	++	+++	±
	5	±	+++	++	±
>10 days		−		+++	++

+++, ++, +, ± and − indicate the relative grades of the findings meaning severe, moderate, mild, trace and no changes, respectively.

weight of the rats before and after UN treatment ($P<0.001$).

Serum creatinine was significantly increased in rats injected with UN 15mg/kg and 30mg/kg as compared to the control (Table 3). The levels in the 5mg/kg treated rats increased after 72 hrs; but they returned to the level of the control after 10 days.

UN significantly increased BUN 24 hrs post injection even in the 5mg/kg treated group (Table 4). The values were further increased after 72 hrs and decreased after 10 days.

However, the levels of calcium and inorganic phosphate in the serum and creatinine in the 24 hr urine showed no significant change after UN treatment (Table 5). Ranges in the levels measured in the male Sprague Dawley rats were the same as those reported by Mitruka and Rawnsley (1981).

Twenty four hrs after UN injection there were no gross changes in the organs. The kidneys appeared pale while the spleen was hyperemic.

The renal sections obtained 24 hrs after UN treatment (Fig. 5 A and B) exhibited partial degeneration of the proximal tubules and many casts in the distal convoluted tubules. Proximal tubular damage and the casts in the distal tubules were increased at 72 hrs (Fig. 5C and D). After the 5th day, we clearly observed regenerating activities in the proximal tubules; they were more evident after the 10th day (Fig. 5 E and F, Table 6). Infiltration of the interstitial inflammatory cells was present after the 10th day (Fig. 5 G).

The ultrastructural alterations of proximal tubular epithelial cells 24 hrs after being treated with UN (5mg/kg) included cytoplasmic hydrophic changes, peripheral margination of heterochromatin in the nucleus, and disappearance of the basal labyrinth. In spite of mitochondrial damage such as an increase in matrix density, dilation of cisternae and hydrophic changes, the microvilli were intact, and the basement membrane was well preserved (Fig. 6A).

With a higher concentration of UN (30mg/kg) the ultrastructural alterations became more defined and severe (Fig. 6 B).

Seventy two hrs post UN injection, many organelles in the proximal tubular cells had ruptured and the microvilli had disappeared. Finally the mitochondrial membrane was ruptured and amorphous dense bodies were deposited in the matrix. However, distal tubular cells, glomeruli and the basement membrane of proximal tubular cells remained intact (Fig. 7 A).

The proximal tubular cells from rats 12 days post UN 30mg/kg revealed regeneration activities and products such as mitosis, short scanty microvilli on the lumen, a very decreased number of organelles, and short epithelium lining (Fig. 7 B). All of these findings indicate that maturation of the cellular organelles followed cellular proliferation.

DISCUSSION

Radiotoxic health hazards from an excessive exposure to uranium and its salts have been recognized for a long time. On the basis of extensive studies associated with the Manhattan project (Tannenbaum *et al.* 1946), it was considered unlikely that ordinary industrial exposure to uranium would pose any significant chemotoxic threat. However, under experimen-

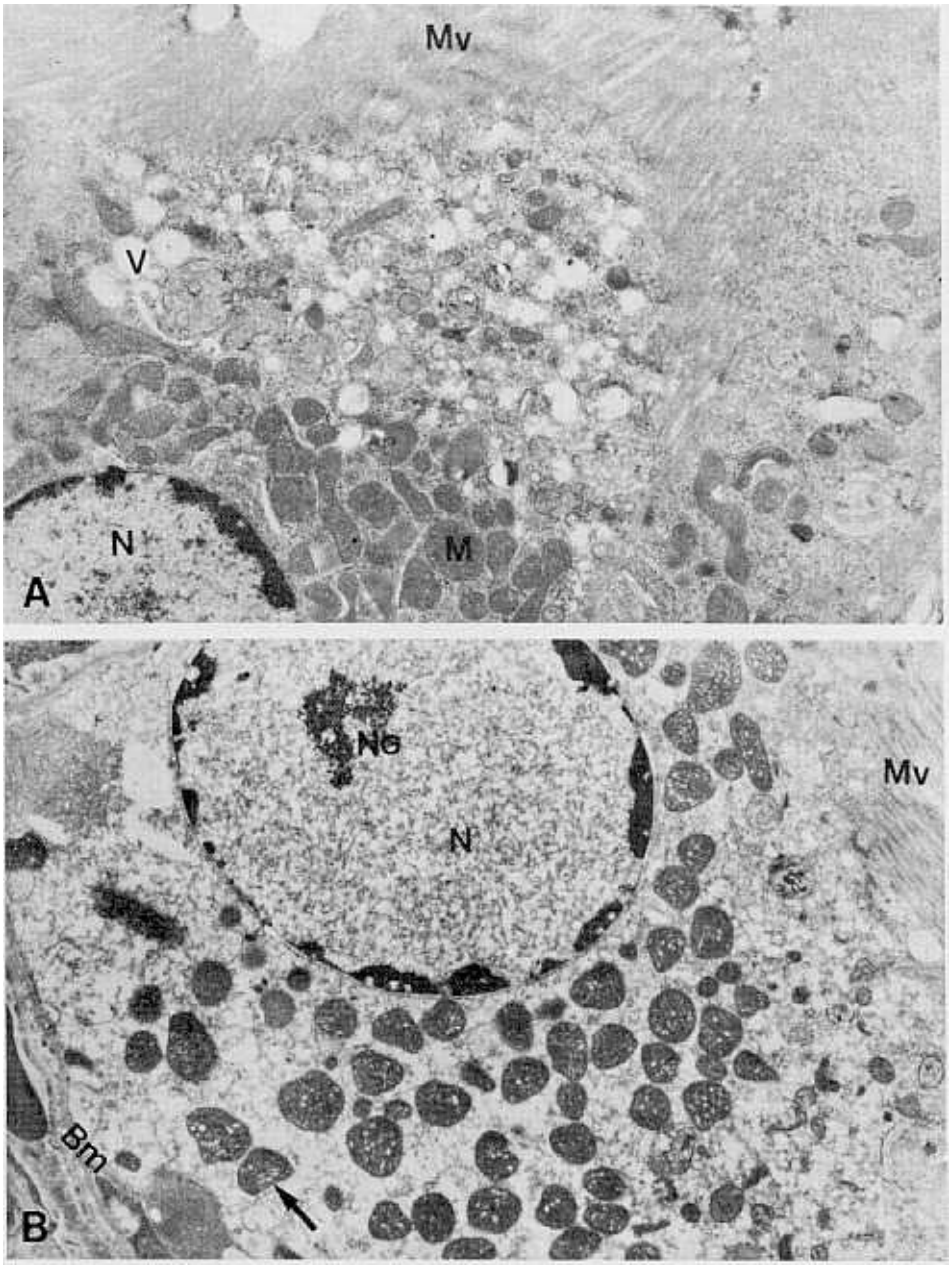

Fig. 6. Electronmicrographs of the proximal tubules from male Sprague Dawley rats after intravenous injection with uranyl nitrate 5mg/kg (A) and 30mg/kg (B) and killed 24 hrs later.

A: Note the hydrophic changes in the apical portion of the cytoplasm, and the small and large vacuoles (V) like the clear spaces. Swollen mitochondria (M) appear as increased electron density with dilated cisternae and clear spaces, × 10,000.

B: Higher concentration of uranyl nitrate induced the increase both in number and size of the cytoplasmic vacuolation and peripheral margination of heterochromatins. We can see the mitochondrial changes (arrow), such as hydrophic degeneration, dilation of cisternae and electron-dense matrix.

Basal labyrinth disappeared 24 hrs after UN injection.

Microvilli (Mv) were intact, × 9000.

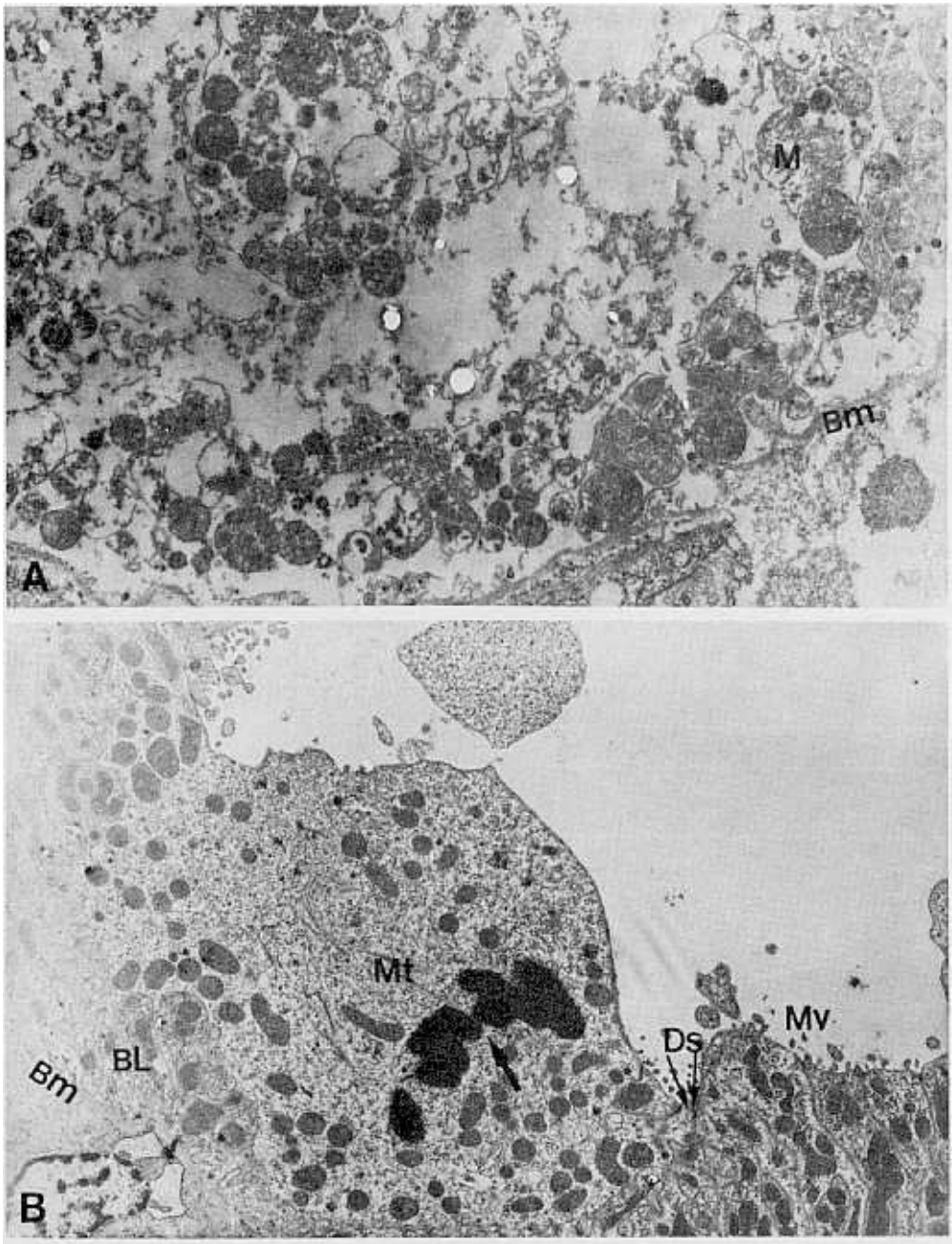

Fig. 7. Electronmicrographs of proximal tubules from rats after injection with uranyl nitrate (30mg/kg) and sacrificed 72 hrs (A) and 12 days (B) later.

A: Note the total destruction of the cytoplasmic organelles: membrane rupture and deposition of amorphous dense bodies in the matrix of the mitochondria (M) and disappearance of microvilli. However, the basement membrane (Bm) is well preserved, × 9000.

B: Observe the relatively short proximal tubular cells undergoing mitosis (arrow) and the microtubules (Mt). Note the markedly decreased number of organelles, the vestiges of short microvilli (Mv) and the appearance of the basal labyrinth (BL) but without the parallel arrangement of mitochondria. Double arrow shows desmosome (Ds). Basement membrane (Bm), × 6666.

tal conditions, uranium is capable of producing renal damage by chemical action (Hodge *et al.* 1973; Voegtline & Hodge 1949). UN has been employed in experiments to produce renal failure characterized by abnormal electrolyte excretion, proteinuria, glucosuria, aminoaciduria, tubular necrosis and eventually anuria (Avasthi *et al.* 1980; Chaudhari & Kirshenbaum 1983; Fukuda & Kopple 1980; Luessenhop *et al.* 1959; Nechay *et al.* 1980; Norberg & Molin 1983). However, diuresis was also observed in uranium nephropathy (Bowman & Foulkes 1970; Maher 1976). The studies investigating the mechanism of renal failure induced by soluble compounds of uranium can be divided into two groups, one is morphological i.e., the reduction of glomerular ultrafiltration due to the loss of endothelial fenestrae (Avasthi *et al.* 1980) and the other is biochemical, i.e., decreased PG metabolism (PGE_2-9-ketoreductase activity, Chaudhari & Kirshenbaum 1983), and inhibition of Na^+-K^+-ATPase by U^{+6} or UO_2^{2+} (Nechay *et al.* 1980).

Characteristics of nephrotoxic ATN caused by a variety of renal poisons including heavy metals (mercury, lead, uranium *et al.*) are acute necrosis in the proximal convoluted tubules, preservation of the tubular basement membrane, and usually intact distal tubular segments with oliguria or anuria (Robbins *et al.* 1980; Solez 1983). In this report, we have described UN induced polyuric ATN in Sprague Dawley rats. The initial stage of ATN is partial degeneration of the proximal tubular epithelium within 24 hrs, followed by frank necrosis until 72 hrs, then active regeneration of the tubular cells is seen after 5 days, and finally dilated tubules lined with epithelial cells are regenerated.

Body weight of the rats decreased 24 hrs after treatment depending on the concentration of the UN; significantly increased water intake and urine output for more than 10 days (Fig. 1-3) was noted. The changes in body weight and water intake provide significant information for predicting the change in urine output of the rats with or without UN treatment ($P<0.001$, Table 2).

ATP and ATPase are involved in ion transport, especially the active transport of Na^+, K^+ and Mg^{++} in the kidney. In the proximal tubule, Na^+-K^+ ATPase activity is strategically located at the peritubular border (Nechay 1977), the site of the active transport of sodium with a passive reabsorption of water and chloride (Smith *et al.* 1983). Through the EM studies, we observed the destruction of mitochondria (Fig. 6 and Fig. 7 A) in the proximal tubular cells 24 hrs after UN injection. Therefore mitochondrial oxidative phosphorylation is inhibited by the injection of UN (5mg/kg or more) and mitochondria in the pximal tubular cells can not supply ATP for the reabsorption of Na^+ and water. Moreover, U^{6+} may inhibit Na^+-K^+ ATPase at the Na^+ site on the enzyme (Nechay *et al.* 1980). These findings are in good agreement with Nechay's proposal (1977) for the biochemical basis of diuretic action in rats. Thus we can suggest a reason for the polyuria and polydipsia (Fig. 2 and 3, Table 1) in rats treated with 5mg/kg or more of UN.

There was a 3 day period of azotemia with a marked increase in BUN level and an increase in serum creatinine accompanied by severe diuresis. The diuresis continued for more than 10 days while the BUN and serum creatinine levels decreased in the 5mg/kg treated rats (Fig. 3 Table 3,4). UN had no effect on the levels of Ca^{++} and *Pi* in serum nor creatinine in the 24 hr urine (Table 5), when compared with the data reported from normal rats (Mitruka & Rawnsley 1981).

Initially, proximal tubular necrosis and the deposition of casts in the distal tubules were more severe in rats injected with a UN dose of 15mg/kg or more, (Fig. 5 A-D). However, the regenerating activities of the proximal tubular epithelium and the interstitial inflammatory cell infiltrations were independent of the concentration of UN (Table 6).

The regenerative changes in the proximal tubular epithelium following acute uranium nephritis observed in our laboratory are in aggrement with Oliver's report (1915). These include, tubular epithelium with large, hyperchromatic nuclei, a dissolved nuclear membrane, free chromatin in the cytoplasm, increased microtubules, and small and large dilated tubules (Fig. 5 E-G and 7 B). These regenerative changes became more pronounced 72 hrs after UN treatment. At the end of the 5 th day, the large nuclei of the tubules have increased in number with a concomitant decrease in necrotic areas. By the 10 th day, there is no sign of necrotic cells in the dilated tubules (Table 6). However, the regenerated epithelium still differs from that of normal tubular cells; it has relatively short cells with a markedly decreased number of organelles, vestiges of short microvilli, and round to oval shaped mitochondria. These findings suggest that the maturation of intracellular organelles follows the regeneration of the premature cells 10 days after UN injection.

REFERENCES

Avasthi PS, Evan AP, Hay D: Glomerular endothelial cells in uranyl nitrate-induced acute renal failure in rats. *J Clin Invest 65:121-127, 1980*

Bieri JG, Stoewsand GS, Briggs GM, Phillips RW, Woodard JC, Knapka JJ: Report on the American Institute of Nutri-

tion Ad Hoc Committee on standards for nutritional studies. *J Nutrition 107:1340-1348, 1977*

Bowman FJ, Foulkes EC: Effects of uranium on rabbit renal tubules. *Toxicol Appl Pharmacol 16:319-399, 1970*

Chaudhari A, Kirshenbaum MA: Mechanism of increased renal prostaglandin E_2 in uranyl nitrate-induced acute renal failure. *Prostaglandins 26:689-699, 1983*

Fukuda S, Kopple JD: Chronic uremia syndrome in dogs induced with uranyl nitrate. *Nephron 25:139-143, 1980*

Hodge HC, Stannard JN, Hursh JB: Uranium plutonium transplutonic elements. *Handbook of Experimental* Pharmacology, Vol. 36, Berlin, Springer-Verlag, 1973

Luessenhop AJ, Gallimore JC, Sweet WH, Struxness EG, Robinson J: The toxicity in man of hexavalent uranium following intravenous administration. *Am J Roentgenol 79:83-100, 1959*

Maher JF: Toxic nephropathy. In Brenner BM, Rector FC, ed. *The Kidney*, Philadelphia, WB Saunders Co., 1976, Vol. 2

Mitruka BM, Rawnsley HM: *Clinical biochemical reference values.* In Mitruka BM, Rawnsley HM, ed. The Clinical Biochemical and Hematological Reference Values in Normal Experimental Animals and Normal Humans, 2nd ed. New York, Masson Publishing USA, Inc., 1981, 153-314.

Nechay BR: Biochemical basis of diuretic action. *J Clin Pharmacol 17:626-641, 1977*

Nechay BR, Thompson JD, Saunders JP: Inhibition by uranyl nitrate of adenosine triphosphatases derived from animal and human tissues. *Toxicol Appl Pharmacol 53:410-419, 1980*

Norberg AB, Molin N: Toxicity of cadmium, cobalt, uranium and zinc to Zoogloea ramigera. *Water Res 17:1333-1336, 1983*

Oliver J: The histogenesis of chronic uranium nephritis with especial reference to epithelial regeneration. *J Exp Med 21:425-451, 1915*

Robbins SL, Cotran RS, Kumar V: *Diseases of tubules.* In Robbins et al ed. Pathologic Basis of Disease, Philadelphia, WB Saunders Co, 1984, 1026-1029

Smith EL, Hill RL, Lehman IR, lefkowitz RJ, Handler P, White A: *Renal regulation of sodium, chloride, and water excretion.* In Smith EL et al ed. Principles of Biochemistry; mammalian Biochemistry, 7th ed. London, McGraw-Hill International Book Co, 1983, 164-168

Solez K: *Acute renal failure.* In Heptinstall RH ed. Pathologies of the Kidney, Boston/Toronto, Little Brown Co., 1983, 1069-1148

Tannenbaum A, Silverstone H, Koziol J: *Manhattan Project Report, CH-3649.* Chicago, Michael Reese Hospital, 1946

Voegtlin C, Hodge HC: *Pharmacology and toxicology of uranium compounds, Books 1 to 4.* New York, McGraw-Hill Book Co, 1949-1953