Production of Experimental Uremia by Sodium Tetrathionate.* (18485)

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Gilman *et al.*(1) indicated that *in vivo* tetrathionate causes proximal renal tubular necrosis, uremia, oliguria or anuria, cast laden urine, and, that with doses of 500 mg/kilo of body weight or less, significant pathology is limited to the kidney. This suggests the use of tetrathionate for producing experimental uremia with fewer non-uremic complications than occur following use of other nephrotoxins, and is the concern of this paper.

Methods and materials. Six percent sodium tetrathionate† ($Na_2S_4O_6 \cdot 2H_2O$) solution was administered intravenously to mongrel dogs in doses of 100-500 mg/kilo of body weight. Morphine sulfate sedation was used when needed. Urines were collected daily, tested for reducing substances, specific gravity (SpG), examined for casts, and the volume noted, during control and uremic periods. Blood non-protein nitrogen (NPN) was determined daily by the Folin-Wu method(2). Carbon dioxide combining power (CO_2CP) was followed in one dog by the Van Slyke method(3). All dogs were sacrificed by intravenous pentobarbital and autopsied. Tissues taken for pathological study were fixed in formaldehyde and Zenker's solution.

Controls. To determine the presence of early, short-lived pathological changes, 3 dogs were given 450 mg of sodium tetrathionate/kilo of body weight, and one dog was sacrificed on the first, second, and third day respectively. Because reducing substances appeared in the urine following tetrathionate administration, fasting blood sugars were determined by the Folin-Wu method(4) in one dog for 3 consecutive days when the urine contained reducing substances. One normal dog was sacrificed to detect pathological changes resulting from pentobarbital administration.

Results. Uremia. Uremia of severity approximately proportional to the dosage of sodium tetrathionate resulted. Some animals responded to lower doses with a more severe uremia than did others to higher doses. Those receiving lower doses usually developed a reversible uremia (Fig. 1). Weight loss due to anorexia and dehydration was evident. Upper respiratory infections contracted during the uremia increased its severity. The CO_2CP fell from 65 vols % to 42 vols % in one animal upon which this determination was performed daily. Convulsions and vomiting occurred in those with severe uremia. One dog, after surviving an upper respiratory infection contracted during the course of its uremia, became chronically uremic, with an NPN which, at the time of writing, has varied from 75-120 mg % for more than 13 months.

Urine. Animals became anuric or oliguric following higher doses of tetrathionate. Urine which appeared was milky, opalescent, and greenish-yellow. It contained casts of all varieties, red, white, and epithelial cells, and reducing substances. The SpG fell to 1007-1011. Control pre-tetrathionate urines were normal.

Blood sugar. On the first 3 post-tetrathionate days, the blood sugar of one dog was 83, 93 and 100 mg % respectively when urines were 4, 4, and 3 plus respectively for reducing substances.

Pathological findings. Gross lesions. The

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1. Gilman, A., Phillips, F. S., Koelle, E. S., Allen, R. P., and St. John, E., *Am. J. Physiol.*, 1946, v147, 115.

† Supplied through the courtesy of Dr. Irwin C. Winter of G. D. Searle and Co., Chicago, Ill.

2. Folin and Wu, *J. Biol. Chem.*, 1919, v38, 81.

3. Van Slyke, D. D., *J. Biol. Chem.*, 1917, v30, 347.

4. Folin and Wu, *J. Biol. Chem.*, 1920, v41, 367.

5. MacNider, Wm. deB., *Scient. Monthly*, 1942, v54, 149.

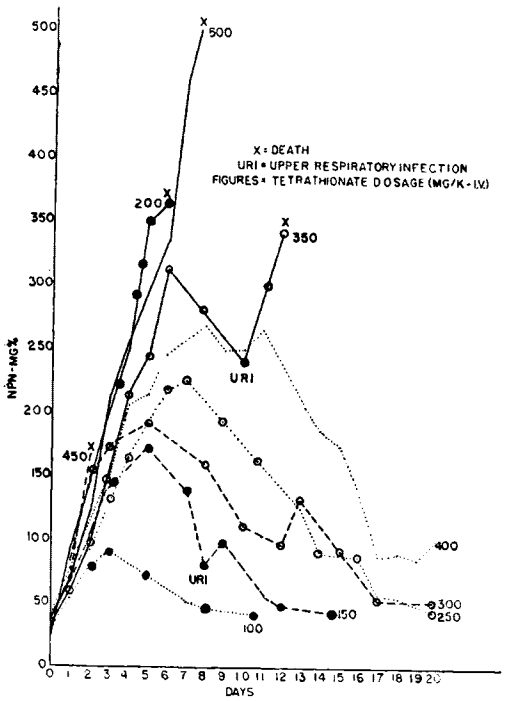

FIG. 1.

Blood NPN following intravenous administration of sodium tetrathionate. Each curve represents a different dog.

gross findings were passive congestion of all viscera, especially the liver and spleen, pulmonary edema and areas of atelectasis. Intussusception with submucosal hemorrhages and necrosis occurred in one animal.

Microscopic lesions.‡ The heart, lungs, liver, spleen, pancreas, adrenals and intestines showed no lesions not attributable to the terminal state, fatal pentobarbital intoxication, or uremia. The kidneys (Fig. 2 and 3) showed some enlargement of the glomeruli due to congestion and/or increased cellularity of the capillary loops, with proteinaceous fluid in a few Bowman's spaces. The majority of glomeruli were normal. The predominant renal lesion was coagulation necrosis with brightly eosinophilic staining cytoplasm and indistinguishable lumen spaces of the proximal convoluted tubules. Calcium deposition in necrotic epithelium was seen in older lesions (Fig. 3). Granularity, karyolysis, fraying, loss of brush border and vacuolar degeneration were present throughout all sections. Pink staining material in the lumina and sometimes only cloudy swelling were observed in milder cases. The lesions of the distal convoluted tubules resembled those of the proximal convoluted tubules, but their severity and extent were not as great. The collecting tubules showed hydropic vacuolization of their upper segments and pink staining material in some lumina. The interstitial tissue and vessels were moderately congested in a few cases.

The significant findings in the acute control animals receiving tetrathionate were confined to the kidneys (Fig. 2) and resembled

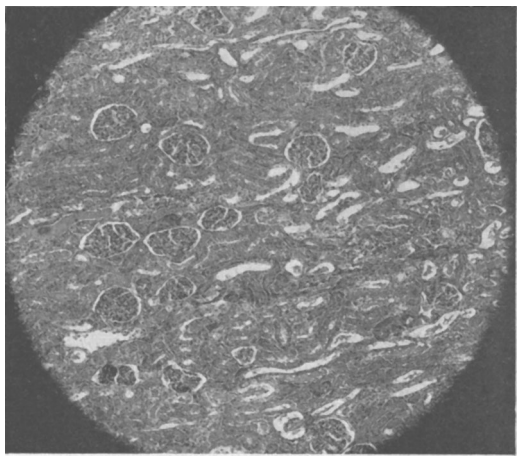

FIG. 2.

Acute renal lesions one day after 450 mg/kilo of sodium tetrathionate were administered intrav.

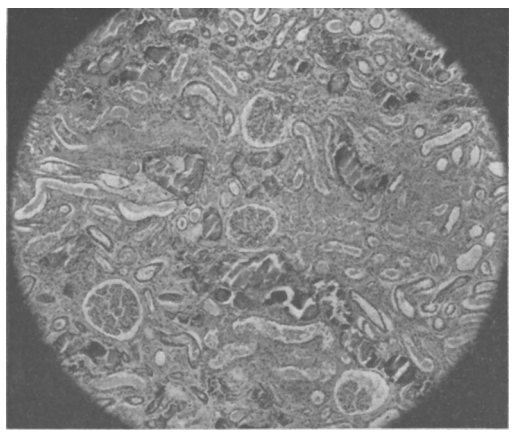

FIG. 3.

Renal lesions 13 days after 363 mg/kilo of sodium tetrathionate were administered intravenously. Note calcification of necrotic tubules.

‡ The author is indebted to Dr. M. Goldenberg of the Pathology Dept., The Chicago Medical School, Chicago, Ill. for these studies.

the findings described above. The pentobarbital control showed slight cloudy swelling of the kidney with casts in many of the loops of Henle. Other organs were normal or showed varying degrees of passive congestion.

Discussion. Surgical methods produce a uremia which is complicated by the dangerous and uncertain post-surgical state. Uremia produced chemically is often complicated by toxic reactions and uncertainty of results. The use of sodium tetrathionate as a nephrotoxin appears to overcome these disadvantages. The cause of the specific susceptibility of the tubule cells to the action of tetrathionate is not yet known. Gilman *et al.*(1) have discussed the possible mode of action of tetrathionate. The fact that the specific lesions produced by tetrathionate are limited to the kidney allows the production of experimental uremia without complications resulting from the technic used. The development of chronic uremia in one dog may have resulted from the contraction of an upper respiratory infection at a time when renal tubular proteins were circulating in the blood stream, with resultant formation of autoantigens and the subsequent development of auto-antibodies specific for the renal tubule.

Although one laboratory procedure, such as an NPN determination, cannot indicate the complete functional status of an organ as complex as the kidney, it can, when performed daily indicate the renal trend. Fig. 1 shows that increasing the dose of sodium tetrathionate from 100-500 mg/kilo of body weight increases the duration and severity of the uremia as indicated by the NPN and incidence of death. Those succumbing to lower doses were older animals; those surviving higher doses were much younger. This is in accordance with the findings of MacNider (5) who demonstrated that older dogs are more susceptible to nephrotoxins than younger ones.

The appearance of urinary reducing substances following tetrathionate administration required the ruling out of a hyperglycemia. In the control animal, fasting blood sugars were at low normal levels when fresh urines gave a 3 or 4 plus reaction with Benedict's solution, indicating that the reducing substances in the urine were due to tubular lesions and not a hyperglycemia.

Summary and conclusions. Uremia was produced in dogs by intravenous administration of varying doses of sodium tetrathionate. The findings of Gilman *et al.*(1) cited above were confirmed. In addition, it was shown that renal lesions resulting from tetrathionate administration, heretofore not described in detail, involve the distal convoluted and collecting, as well as the previously mentioned (1) proximal renal tubules. The resulting uremia may be rapidly fatal or continue 20 or more days, and is accompanied by non-hyperglycemic urinary reducing substances and lowered CO_2CP and SpG of the urine. The mechanism of chronicity following uremia complicated by an upper respiratory infection is briefly discussed. The specific action of tetrathionate on the kidney and the freedom from non-uremic complications following its use demonstrates its efficacy for producing experimental uremia.

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Reversible Inhibition of Growth of *Microsporum audouini* with Neopyrithiamine.* (18486)

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Recent studies of the nutritional requirements of certain fungi have definitely established the essential nature of certain metabolites for growth and formation of spores. It has been shown that certain fungi are unable to synthesize these essential metabolites