THE NEPHROTOXIC ACTION OF SODIUM TETRATHIONATE

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PREFACE

The publication in 1946 of the results of a study by Alfred Gilman and his associates in whic sodium tetrathionate was found to produce damage to the dog and rabbit nephron led the Council on Pharmacy and Chemistry of the American Medical Association to recommend that the use of this drug in medicine be abandoned. The leading proponent of the use of sodium tetrathionate in the treatment of peripheral vascular disorders, Dr. Frank V. Theis, protested this recommendation on the basis that the doses used by Gilman were far in excess of those used clinically, and that these low clinical doses had been used for many years without serious complications. The Council on Pharmacy and Chemistry thereupon amended its first statement so that it did not condemn the use of tetrathionate but emphasized that it be used with caution in the knowledge of its possible effects on renal function.

In view of the great difference between the dosage range used by Gilman in his animal studies (100 - 500 mgm./kgm.) and that used by Theis in his clinical work (7 - 8 mgm./kgm.), it seemed desirable to investigate the nephrotoxic action of sodium tetrathionate in the intermediate dosage range (10 - 100 mgm./kgm.).

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HISTORICAL

The development of modern concepts of renal physiology owes its initial gain to Malpighi's discovery in 1666 that the medullary striae are not fibers, but are actually minute tubes continuous with the globular "glandular" structures or glomeruli. Some 200 years later, Bowman was able to offer proof of Malpighi's early discovery (1). Bowman assumed that urinary wastes are excreted through the epithelium into the tubular lumens. The function of the glomerulus was supposed to lie solely in providing water to flush down the contents of the tubules. Later, Heidenhain postulated that in addition to water there are salts that pass through the glomerular membrane into the tubules (2). Ludwig, however, (3) favored the theory that urine is composed solely of glomerular filtrate, with concentration occurring via tubular reabsorption of water. These conflicting views were more or less adhered to by different renal physiologists until Cushny postulated his theory of filtration-reabsorption (4). Briefly stated, this theory proposed that urine is composed of the glomerular filtrate minus those components which are reabsorbed selectively across the tubular epithelium into the peritubular capillaries. The new premise of this theory was that the glomerular filtrate is identical in composition with the plasma except for the absence of the plasma proteins, to which the glomerular capillaries were presumed to be impermeable. Richards and his co-workers have investigated the composition of the glomerular fluid in the frog and other cold-blooded animals (5,6,7), and have produced evidence that in these species the only important constituents of the plasma that do not pass freely through the glomerular membrane are fats

and plasma proteins, or substances chemically combined with these. Further, by comparing the composition of the capsular fluid with that of the urine, these investigators demonstrated the reabsorption of substances such as glucose and chloride as evidence for the actuality of tubular reabsorption. The evidence for excretion by tubules has been reviewed by Shannon (8) and it has been established that in man, tubular excretion plays a very important part in the excretion of phenol red (9), diodrast, hippuran (10,11) and creatinine (12,13) to mention a few of the compounds which have been studied.

Once it has been recognized that tubular excretion does in fact occur, it is obvious that in order to investigate further the quantitative aspects of renal function it is necessary to have a substance available which is known for certain to be neither excreted nor absorbed by tubular processes. With this substance as a standard of reference, tubular reabsorption of water could be measured and, consequently, the path of excretion of any other substance could be identified. A long series of studies has led to the use of inulin (14), a starch-like polysaccharide composed of 32 hexose molecules with a total molecular weight of 5200 (15). This substance is completely filtrable from plasma through a collodion membrane and is excreted by most animals by glomerular filtration without tubular participation. This being true, it then follows that the extent of water reabsorption is given by the ratio between the inulin concentrations in urine and plasma (U/P), and that the glomerular filtration rate is equivalent to the quantity of inulin excreted per minute (UV) divided by the concentration in each milliliter of plasma (P).

In seeking an empirical means of describing rate of excretion of urea (which varies with the rate of urine flow) Moller, McIntosh and Van Slyke introduced the term "clearance" in 1928 (17). This term was used by these authors to denote the volume of blood depleted of urea by one minute's excretion of urine. This concept was found so useful that since the original work by Van Slyke and his associates the term "clearance" has been applied to many compounds and, in general, denotes the virtual volume of blood (or more strictly, plasma) completely cleared of the reference substance by urinary excretion each minute. From what has been said above it is clear that the inulin clearance is equal to the glomerular filtration rate (GFR). Similarly it follows that substances, the clearances of which are less than that of inulin (such as Na, K, Cl, amino acids, glucose and ascorbic acid), if filterable through the glomeruli, must be reabsorbed by the tubules; substances with clearance values higher than that of inulin (such as phenol red, hippuran and diodrast) must be excreted by the tubules (18).

Changes in the plasma concentration of inulin have no effect on the inulin clearance (16), since no matter how little or how great the amount of inulin present in the glomerular filtrate, it is passed on into the urine (19,20). But this does not hold for substances which are excreted or reabsorbed by the tubules. In the case of glucose, for example, there is a maximal rate at which the tubular cells can remove glucose from tubular urine. As the concentration of glucose in the glomerular filtrate is increased, more and more glucose is presented to the tubules for reabsorption until a point is reached when the reabsorption rate is maximal. Whenever glucose is filtered more rapidly than its maximal rate of tubular reabsorption, it appears in voided

urine. The maximal reabsorption rate (Tm) has been measured in many animal species; in man it averages 375 mgm. glucose per minute (18). Similarly, for substances that are excreted by the tubules, there is a maximal quantity which can be handled by the tubule cells per unit time. As a corollary to these observations, it should be apparent that once the maximal tubular reabsorption or excretion values have been reached for a given substance, then the clearance of this substance becomes independent of its concentration in the plasma.

From the foregoing principles it can be seen that by estimating values of glomerular filtration, tubular reabsorption and tubular excretion of certain substances, it should be possible to evaluate the renal activity of the animal kidney before and after application of any stress. Such studies on the rabbit after poisoning with sodium tetrathionate will constitute the main theme of this paper.

INTRODUCTION

Acute renal failure may occur in a wide variety of circumstances, among which may be included shock, disturbances in electrolyte balance, pigment excretion, allergy and chemical intoxication (21). The nephrotoxic action of chemicals can be ascribed largely to damage to the proximal segments of kidney tubules. Hayman, Shumway, Dunke, and Miller (22) found that in dogs, uranium poisoning causes a decrease in the inulin, creatinine, and urea clearances. The authors attributed these reductions in clearances to back diffusion of all urinary constituents. Laake (23) examined the effects of uranyl nitrate in rabbits and observed reversible reductions in inulin and diodrast clearances in surviving animals. The author concluded that uranium impairs the function of the proximal tubule, and if sufficient damage is incurred it is accompanied by reabsorption of inulin and all other constituents of the tubular urine.

Salts of tartaric acid produce damage to the proximal tubule without affecting the glomeruli (24). Tartrate intoxication is accompanied by a reduction of the urea, xylose, creatinine, inulin, and phenol red clearances (25). Mercury also produces necrosis of the proximal tubule, the lowest portion being most affected in the human, rabbit or rat kidney (24). Severe intoxication with mercury induces glucosuria (26), as does uranium and bichromate poisoning. Bichromate produces a nephrotoxic effect similar to that of mercury and uranium, but affecting the upper rather than the lower portion of the proximal tubule. In rabbits poisoned with bichromate, Schou (27) observed reductions in creatinine clearance and in the creatinine U/P ratio.

Potassium chlorate and potassium bromate also produce necrosis of the proximal tubule (2).

In 1936, Rabinowitz (31) and Rabinowitz and Kahn (32) introduced the use of thiosulfates in the treatment of thromboangiitis obliterans. Bancroft, Stanley-Brown, and Chargaff (33) studied the effect of sodium thiosulfate on the clotting index of the plasma and fibrinogen content of the blood and concluded that morbidity due to postoperative thrombophlebitis could be reduced by the prophylactic injection of sodium thiosulfate (combined with a low fat and protein diet).

In 1939, Theis and Freeland (34-37) proposed the use of sodium tetrathionate in place of sodium thiosulfate in the treatment of thromboangiitis obliterans on the assumption that the toxicity of tetrathionate and that of thiosulfate were essentially the same. The usual intravenous doses used were 1.0 gm. of sodium thiosulfate and 0.885 gm. of sodium tetrathionate and no signs of toxicity were reported.

In a study of the mechanism of excretion of sodium tetrathionate by the dog kidney it was discovered by Gilman, Philips, Koelle, Allen and St. John (28) that tetrathionate is rapidly reduced to thiosulfate in vivo and that tetrathionate is sufficiently toxic to the renal tubule for moderate doses to produce complete anuria within less than an hour. These authors injected sodium tetrathionate (in doses ranging from 100 mgm. to 500 mgm. per kilogram body weight) into anesthetized, catheterized dogs and found that anuria develops within 30 to 60 minutes. Pathological examination of the kidneys revealed severe necrotizing lesions of the proximal tubule. In view of their experimental evidence that tetrathionate can be reduced in vitro with 2,3-dimercaptopropanol,

l-thiosorbitol, cysteine, and glutathione, with the stoichiometric formation of the corresponding disulfides, and that the prophylactic administration of l-thiosorbitol or cysteine protects against the nephrotoxic action of tetrathionate, these authors postulated that 1, tetrathionate selectively permeates the cells of the proximal tubule to exert a direct toxic action on catalytic systems dependent on the presence of sulfhydryl groups, or 2, the cells of the proximal tubules are selectively damaged by the removal of diffusible sulfhydryl compounds.

Goffart and Fischer (29) have studied the rate of reaction of sodium tetrathionate with the sulfhydryl groups of glutathione, cysteine, and proteins in vitro as well as the reaction with the sulfhydryl functions of rabbit kidney and muscle. As a result of these studies the authors concluded that tetrathionate intoxication produces a greater depletion of reduced glutathione in the kidney (77%) than in the blood (28%), the liver (30%) or muscle (20%). Gilman's hypothesis (28) that diffusible, reduced glutathione is drained from the tissues into the blood was confirmed. In addition, it was found that since tetrathionate passes through the glomerular membrane, the consequent high concentration in tubular urine affects the cells of the convoluted tubules. The findings of Gilman (28) were also confirmed by Sloan (30) who produced uremia in dogs by the intravenous administration of sodium tetrathionate in doses of 100-500 mgm./kgm. of body weight. Sloan also showed that renal lesions resulting from tetrathionate poisoning involved the distal convoluted and collecting tubules as well as the previously reported (28) proximal tubules.

In view of the work of Gilman and his associates (28) the Council on Pharmacy and Chemistry of the American Medical Association (38)

recommended that the use of sodium tetrathionate in medicine be abandoned. Following this recommendation, Theis (39) protested to the Council and pointed out that the doses used in his work (approximately 7 mgm./kgm.) were much lower than those used by Gilman in his experimental studies (100-500 mgm./kgm.). From an analysis of Gilman's reported observations, Theis stated that tetrathionate, when used in doses comparable to those used clinically, is not toxic to experimental animals, and that the delay in eliminating tetrathionate from the body (as opposed to the relatively short time required for thiosulfate elimination) is not sufficiently delayed to produce a toxic cumulative effect from daily injections. Theis concluded his protest by advising the Council to reconsider its recommendation that the use of tetrathionate in medicine be abandoned, in view of the absence of any clinical or laboratory evidence of toxicity in the doses recommended. A statement to the same effect was also submitted by de Takats (40). In view of these two protests, the Council on Pharmacy and Chemistry amended its previously published recommendation (38) by printing the following statement (41):

> No nephrotoxic effects were observed in the patients treated by Dr. Theis and his associates and apparently these investigators feel that there is little if any danger of such effects from the doses that they have used clinically. However, when an agent is capable of interfering with the important but insufficiently known SH functions, a word of caution is not amiss. It should be realized at least that the dosage must be kept at a minimum and the renal function kept under close observation. Further observations may reveal additional valuable information.

Since the publication of this statement, there have been at least two reports of the use of sodium tetrathionate in humans. Winsor (42) studied the rate of blood flow to the digits in normal subjects and in

those with arteriosclerotic obliterative disease after injection of 0.6 gm. sodium tetrathionate. He concluded from this study that indirect heating is more efficacious in increasing the flow rate and skin temperature than sodium tetrathionate. No studies were made of the possible effects of sodium tetrathionate on renal function.

Bloom, Forbes and Policoff (43), in an effort to determine the toxicity of tetrathionate clinically, administered 0.6 gm. of the sodium salt twice daily for a period of seven days to a group of 30 patients, some with peripheral vascular disease and others with various other maladies. Studies of non-protein nitrogen, Rosenthal concentration, and phenolsulfonphthalein excretion were made before and after the course of treatment. After subjecting their data to statistical analysis the authors concluded that for the dosage used, sodium tetrathionate does not materially affect kidney function as regards the non-protein nitrogen and Rosenthal tests. However, it was admitted that the results obtained in the phenolsulfonphthalein excretion tests might be interpreted as definitely reflecting some changes in kidney function. On the basis of these clinical studies the authors state that "it would seem that sodium tetrathionate probably should not be used if there is any pre-existing renal disease".

In view of the great difference between the dosage range used by Gilman (28) in his animal experiments (100-500 mgm./kgm.) and that used by Theis (39) in his studies on humans (7-8 mgm./kgm.), it seemed desirable to investigate the nephrotoxic action of sodium tetrathionate in rabbits in the intermediate dosage range (10-100 mgm./kgm.).

EXPERIMENTAL

Preliminary Experiments. The findings of Breedis, Flory and Furth (44) that uranyl nitrate injection resulted in elevation of the urinary concentration of alkaline phosphatase and in depression of the renal concentration suggested to Bounce (45) that breakdown of kidney tubular cells in uranium poisoning should result in the appearance in the urine of many or all of the intracellular enzymes of the tubular cells. Because catalase occurs in the kidney in high concentration, it seemed that its appearance in the urine might constitute a very sensitive and early indicator of uranium action on the nephron. If the urinary protein is also studied along with the catalasuria, an indication of the effect of any toxic agent on the nephron may be obtained. According to Bounce (45): "A substance having a direct effect on the glomerulus would be expected to produce proteinuria before catalasuria; if the effect were confined to the glomerulus there would be no appreciable catalasuria in the absence of hemoglobin from the urine. A substance affecting both glomerulus and tubule, such as dichromate, would have a high ratio between the simultaneous urinary levels of protein and catalase, whereas more purely tubular poisons, such as uranyl salts, mercuric salts, arsenicals, and tartrates would have low values of this ratio".

In view of this, Wills (46) suggested that if, as Gilman (28) has reported, sodium tetrathionate exerts its action primarily on the tubules, determinations of urinary catalase and protein in tetrathionate poisoned rabbits should reveal an early appearance of catalase followed by proteinuria.

Accordingly, exploratory studies were made of catalasuria and proteinuria in rabbits after poisoning with sodium tetrathionate. Rabbits of mixed breed and sex were used for these studies. It was soon found that many of the rabbits available for these experiments possessed varying degrees of catalasuria and proteinuria, so therefore, an attempt was made to select animals without pre-experimental proteinuria. Catalasuria was almost universal in our rabbits, this finding leading to abandonment of this line of investigation.

Five rabbits, selected as described above, were given intravenous injections of sodium tetrathionate (see Appendix B) into a marginal ear vein. Four animals received 75 mgm./kgm., and one, 25 mgm./kgm. At various times after the injections samples of urine were obtained by manual palpation of the bladder, the urine being collected in a clean beaker. The urine so obtained was then analyzed for catalase by the method of Dounce (47) and for protein by the method of Kingsbury, Clark, Williams and Post (48). A description of the Dounce method for catalase is given in appendix C.

One rabbit was given multiple injections of sodium tetrathionate over a period of seven days, 75 mgm./kgm. being given on the first and fourth days, and 100 mgm./kgm. on the fifth and seventh days. Protein and catalase determinations were done on the urine after each injection. The animal was sacrificed at the end of the eighth day.

Clearance Experiments. Because the results of the preliminary experiments outlined above were inconclusive, it was decided to employ clearance techniques for the further analysis of the nephrotoxic action of sodium tetrathionate. To this end, inulin clearance was used as a measure of glomerular filtration rate, para-aminohippurate clearance as

a measure of tubular excretory mass and glucose and chloride clearances as a measure of tubular function.

The animal was infused intravenously through a polyethylene tube inserted into a femoral vein with 25 ml. of infusion fluid per kilogram of body weight given in a period of 30 minutes. The fluid consisted of a 0.9 per cent solution of sodium chloride containing 0.25 per cent of inulin and 1.6 per cent of sodium para-aminohippurate (PAH). After 30 minutes the infusion rate was reduced to one ml. per minute and continued at this rate throughout the experiment. The infusion fluid was driven by a calibrated Brewer pipetting machine (A. S. Aloe and Company). A short in-dwelling catheter was placed in the bladder (under local procaine anesthesia) and tied in place. Urine was collected continuously without resort to washing. Blood samples were obtained from a polyethylene cannula fixed in a femoral artery.

Clearance periods were fifteen minutes in duration. The urine was collected in a 10 ml. graduated cylinder from the in-dwelling catheter, a blood sample being withdrawn from the femoral artery at the mid-point of the clearance period. Two clearances were determined at 30 minutes and 15 minutes, respectively, before injection of the sodium tetrathionate. Clearances were then determined at 30 minutes and one hour after injection. Additional determinations were made at 2 and 3 hours after injection of the drug. In some experiments, additional clearances were done. A summary of the experiments is given in table 6.

The blood and urine samples were analyzed for inulin by the method of Roe, Epstein and Goldstein (49). Corrections for blood glucose were made by deducting blank values obtained with the animal blood before infusion of inulin was begun. Para-aminohippurate was determined by

the method of Smith, et al. (50); glucose, by the method of Nelson (51) and Somogyi (52); and chloride, by the method of Fister (53).

A total of 19 rabbits of mixed breed and sex were used in this study. Of these, three received a dose of 100 mgm./kgm. of sodium tetrathionate; one, 90 mgm./kgm.; one, 80 mgm./kgm.; one, 70 mgm./kgm.; two, 75 mgm./kgm.; one, 60 mgm./kgm.; three, 50 mgm./kgm.; one, 35 mgm./kgm.; four, 25 mgm./kgm.; and two, 10 mgm./kgm.

Calculation of various measures of renal function. The analytical data and the figures for rate of urine flow were used to calculate the various clearances and other measures of tubular function. A summary of these calculations follows.

Glomerular filtration rate (GFR). Inasmuch as inulin is neither excreted nor absorbed by tubular processes (14), the glomerular filtration rate is given by the inulin clearance, which is the quantity of inulin excreted per minute divided by the concentration in each milliliter of plasma, or,

$$\frac{U_I V}{P_I}$$

Here U_I is the concentration of inulin in the urine, V is the rate of urine flow, and P_I is the concentration of inulin in the plasma. Glomerular filtration rate is given in terms of milliliters per minute. Similarly, the clearances of para-aminohippurate, chloride, and glucose were calculated by dividing the quantity of substance excreted per minute by the concentration in each milliliter of plasma.

Para-aminohippurate clearance. Sodium para-aminohippurate (PAH) is the sodium salt of the para-amino homolog of hippuric acid and is excreted by the tubular epithelium in addition to being filtered by the glomerulus (50). At low plasma concentrations (1.0 to 2.0 mgm./100 ml.),

88 per cent of this compound is removed from the renal blood stream in man by the kidneys in a single circulation (50,54), and the PAH clearance is a rough measure of effective renal plasma flow. In the experiments reported here, however, it was necessary to maintain the plasma PAH at concentrations in excess of 0.6 mgm./ml. for the determination of tubular excretory mass (see below), so that clearances at these high concentrations do not represent renal plasma flow. Nevertheless, the clearances were calculated as an additional overall measure of renal function.

Tubular excretory mass (TEM). As a measure of the functional capacity of the tubular excretory mechanism PAH is used at plasma concentrations above the level at which the maximal capacity of the tubule cells to excrete PAH is reached (50). In addition to being excreted by the tubules, PAH is filtered through the glomerulus, so in order to determine the amount of tubular excretion of PAH, the amount which is filtered must be subtracted from the total amount of PAH excreted. The quantity of PAH filtered through the glomeruli is given by the product

$$GFR \times P_{PAH} \times 0.83$$

where GFR is the filtration rate, or inulin clearance; P_{PAH} is the concentration of PAH in the plasma; and 0.83 is a factor that takes into account the circumstances that some PAH is bound to plasma protein and hence is not available for filtration (50). The total rate of PAH excretion is given by the product of the urinary PAH concentration and the rate of urine flow ($U_{PAH}V$), hence

$$TEM = U_{PAH}V - GFR \cdot P_{PAH}\ 0.83$$

Tubular excretory mass is expressed in milligrams per minute.

Other measures of tubular function. The amount of chloride or glucose excreted in the urine is calculated from the expression

$$UV$$

where U is the concentration of chloride or glucose in the urine, and V is the rate of urine flow; while the amount filtered through the glomeruli is calculated from the expression

$$P \times GFR$$

where P and GFR have the usual significance. It follows that the amount of material reabsorbed is given by the difference between the amount filtered and the amount excreted in the urine, or

$$P \times GFR - UV$$

A more compact measure of tubular function is the ratio of the amount of substance transferred across the tubular membrane to that transferred across the glomerular one. This is designated as fCl or fgl (55). If the expression for inulin clearance $\left(\frac{UIV}{PI}\right)$ is used in place of GFR the expression for fCl (or fgl) can be derived as follows:

$$fCl = \frac{P_{Cl} \cdot \frac{U_I V}{P_I} - U_{Cl} V}{\frac{U_I V}{P_I} \cdot P_{Cl}}$$

$$fCl = 1 - \frac{U_{Cl}\, P_I}{U_I\, P_{Cl}}$$

For substances that are nearly completely reabsorbed by the tubules, the f value should approach 1. In this case, a decrease in the f value would denote interference with tubular function.

RESULTS

Catalasuria and proteinuria studies. The urinary catalase and protein values in rabbits after poisoning with tetrathionate are given in table 1-5. As can be seen, all the rabbits used, with the possible exception of rabbit #1A contained relatively large amounts of urinary catalase prior to the injection of sodium tetrathionate, which makes it extremely difficult to interpret the data. In the case of rabbit 1A, the urinary catalase rose from a pre-injection value of 45 mm^3O_2 per 0.2 ml. of urine to 214 in 4 hours. At this time the urine remained protein free. After 6 hours, the urinary catalase had increased to a value of 2540, but by this time protein had appeared in the urine (35 mgm. per 100 ml.). In rabbit #5, after a dose of 75 mgm./kgm. tetrathionate, the urinary catalase increased over a hundred fold within 3 hours; in this animal urinary proteins also reached a high level (300 mgm./100 ml.) within the same time.

At a lower dose of tetrathionate (25 mgm./kgm.), protein never appeared in the urine in significant amounts, but the catalase values were actually less than the pre-injection figures. Rabbit #3 received multiple doses of tetrathionate over a seven day period. On the first day, after an injection of 75 mgm./kgm. tetrathionate, both urinary catalase and protein increased to high levels but returned to normal after 71.5 hours. On the fourth day, the same dose of tetrathionate was given, and this time there was a decrease in urinary catalase to zero and only a very slight increase in urinary protein. On the fifth day, after 96.5 hours, the urinary protein remained at 25 mgm./100 ml. At 97.5 hours (on the fifth day), 100 mgm./kgm. tetrathionate was given,

which elicited no immediate increase in excretion of catalase and protein. After 1½ hours, however, the urinary protein had increased tremendously (over 1 gram per 100 ml.), although the urinary catalase had increased only slightly over the previous days' value. A further injection of 100 mgm./kgm. tetrathionate did not change the pre-injection values.

Clearance experiments. The results of clearance studies on 19 rabbits are given in tables 7-63. These tables are arranged in sets of 3 tables for each rabbit. The first table in each set (tables 7, 10, 13 ..etc.) gives the analytical values for rate of urine flow and for plasma and urinary concentrations of inulin and PAH, and, where done, the plasma and urinary glucose and chloride values. The second table in each set (tables 8, 11, 14 ..etc.) shows the calculated data obtained from the analytical values. These include GFR (glomerular filtration rate or inulin clearance, PAH clearance, TEM (tubular excretory mass), glucose clearance, glucose excretion, glucose reabsorption, fgl (the ratio of the amount of substance transferred across the tubular membrane to that transferred across the glomerular one), chloride clearance, chloride excretion, chloride reabsorption, and fCl. The third table in each set (tables 9, 12, 15 ..etc.) shows the data for the various renal functions calculated in terms of per cent of the mean control (pre-injection) values. These values were computed in order to facilitate comparison among rabbits given different doses of tetrathionate.

Except for fgl and fCl, the range of values of the various pre-injection renal function ratios was quite wide and this was another reason why the data were calculated in terms of per cent of the pre-injection values, each animal being considered as an individual with

a unique "normal" renal function.

In order to evaluate the nephrotoxic effect of tetrathionate at various dosages, it was decided to compare some of the clearance data obtained 2 hours after injection with the data obtained in the clearance determinations made prior to the injection of tetrathionate, the urine rates for these two periods being not materially different. To make this comparison, plots of $\frac{\text{2 hour value} \times 100}{\text{control value}}$ against dose were made for GFR, TEM, fgl, and fCl. These are shown in figures 1-4.

Figure 1 portrays the reduction in GFR as the dose of tetrathionate is increased. There is some indication that even at a dose of 10 mgm./kgm., a reduction in GFR occurs; as the dose is increased the GFR falls rapidly to levels of about 15 per cent of the pre-injection value at 100 mgm./kgm. tetrathionate.

A similar picture is seen when TEM is considered, except that the depression in TEM is so much more marked that it reaches values of around 10-15 per cent of the pre-injection value at 60 mgm./kgm. tetrathionate (figure 2).

When the tubular function with respect to glucose transport is considered, slightly different behavior is seen. This is shown in figure 3. Here the 10 mgm./kgm. dose of tetrathionate appears to have little effect, and the progressive depression of fgl is much more gradual than that of either GFR or TEM. In one animal (rabbit #68) there was an exceptional decrease in fgl at a dose of 50 mgm./kgm.

In the case of chloride transport, there is seen an even more gradual decline in fCl (figure 4). Here no appreciable depression is seen until the 75 mgm./kgm. dose is reached, and even then the depression is only 50 per cent of the pre-injection value. The 10 and 25 mgm./kgm. tetrathionate doses apparently produce no significant change in fCl.

DISCUSSION

The variability of the data obtained in the catalasuria and proteinuria studies is such that little can be concluded from this work. There is some indication that in one or two cases, catalasuria occurs before proteinuria (rabbits 1 and 1A), but the evidence is not good enough for any conclusions to be drawn. In uranium poisoning, catalasuria reaches its peak more promptly than proteinuria and returns to normal more quickly, also the urinary catalase increases to a relatively greater degree than does urinary protein (47). Predominantly tubular poisons such as mercuric chloride and sodium tartrate produce a similar relation between the increments of urinary catalase and protein (47). In one of the animals studied here (rabbit #8), 26 hours after the injection of 25 mgm./kgm. of tetrathionate, the urinary catalase was 2½ times the pre-injection value, while the urinary protein was zero. This apparently represents a mild action on the tubules causing a slight escape of catalase from the tubular epithelium without a concomitant release of protein.

Although the data obtained were not clear-cut, the effect on the catalase and protein excretion was more or less equal. This finding is not inconsistent with the view that the glomeruli and proximal tubules are almost equally affected by low doses of tetrathionate.

From an examination of the clearance data, it is apparent that doses of sodium tetrathionate as low as 25 mgm./kgm. effect some changes in the renal functions of the rabbit. At this dose, the glomerular filtration rate and tubular excretory mass appear to be depressed to approximately the same degree, while the tubular transfer of glucose

is only mildly affected and the transfer of chloride, not at all. At doses of tetrathionate of 35 mgm./kgm. and above the TEM becomes drastically affected, much more so than the GFR which only reaches similar depressed levels at a dose of 75 mgm./kgm. These data suggest that at low doses of tetrathionate, the glomeruli and the proximal tubules are about equally affected. As the dosage is gradually increased, the primary site of damage is the proximal tubule.

The data on tubular transport of chloride and glucose may indicate the locus operandi of tetrathionate as the dosage is increased further. The fact that at doses up to 50 mgm./kgm. the reabsorption of chloride is only mildly affected as compared with the reabsorption of glucose suggests that the action of tetrathionate at low doses is restricted to the proximal convolution of the nephron. As the dosage is increased, however, the reabsorption of chloride decreases markedly, which is indicative, perhaps, of a gradual involvement of the rest of the nephron. These conclusions are based on evidence that chlorides are partly reabsorbed in the distal segment of the tubule and that glucose is reabsorbed almost completely in the first half of the proximal convolution (56). Additional evidence for gradual involvement of the distal tubules is the finding of Sloan (30) that renal lesions resulting from tetrathionate poisoning involve the distal convoluted and collecting tubules as well as the proximal tubules.

It is desirable at this time to point out that in rabbit #76 (tables 61-63) an extremely low pre-injection value for urinary PAH was obtained. There was no apparent explanation for this fact. The other pre-injection values for this animal were within the usual range except that the chloride clearance was rather high and the fCl somewhat

low. In this case one can only invoke the notorious variability of the rabbit in experimental procedures, which Smith (24) ascribes to the high degree of autonomic instability of that animal.

In three cases (tables 14, 26, 38), TEM fell to a negative value, indicating the complete replacement of tubular secretion by some back tubular diffusion (57). The negative values of fgl (tables 8, 11, 14, 38) and of fCl (tables 11, 14) obtained in some rabbits indicate that tubular reabsorption of glucose and chloride has been blocked completely, and some other phenomenon occurs which appears to represent secretion of these compounds. This does not imply any dynamic activity of the tubules, but rather some process of reverse diffusion through the tubular epithelium analogous to the back diffusion of TEM mentioned above.

In view of the data presented here it seems desirable to re-examine the question of the use of tetrathionate in humans for the treatment of peripheral vascular disorders. At the lowest dose used in this study (10 mgm./kgm.) there was only a moderate decrease in inulin clearance and in tubular excretory mass as determined with para-aminohippurate. That this is probably a transitory phenomenon is attested to by the fact that rabbits injected intravenously with 100 mgm. of tetrathionate (body weight unstated) daily for twelve days (a total dose of 1.2 gm.) showed no ill effects, thrived and gained weight (39). Autopsy study revealed no evidence of nephrotoxic or any other toxic effect. Since the average dose of tetrathionate recommended by Theis (39) is only 7 mgm./kgm., it would seem that no permanent nephrotoxic action could be expected in the normal clinical use of this compound, provided that, as Bloom, Forbes, and Policoff have pointed out (43), there is no evidence of pre-existing renal disease.

SUMMARY

1. Renal function tests were performed on rabbits before and after intravenous administration of doses of sodium tetrathionate ranging from 10 to 100 mgm./kgm. Preliminary studies on the appearance of catalasuria and proteinuria after tetrathionate poisoning were also made.

2. The 10 mgm./kgm. dose had no appreciable effects on tubular transport of glucose and on tubular transport of chloride. It did decrease the tubular excretory mass (hippurate) and glomerular filtration rate (inulin) to some extent.

3. Higher doses of tetrathionate produced decreases in all these variables. The 100 mgm./kgm. dose lowered inulin clearance to about 10 per cent of the control value, tubular transport of chlorides to about 20 per cent, tubular excretory mass to 5 per cent and tubular transport of glucose to zero.

4. The data obtained by renal clearance techniques suggest that low doses of tetrathionate affect the glomerulus and the proximal tubule about equally. At higher doses of tetrathionate, the proximal tubule becomes more seriously affected. As the dose of tetrathionate is increased still further, the distal tubule becomes involved also. The few studies of urinary catalase and protein excretions are not inconsistent with this idea.

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APPENDIX A

TABLES AND FIGURES

Table 1

Catalasuria and Proteinuria in Rabbits

Rabbit #1 Sex - Male Weight - 2.7 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v.

Time (hrs.)	Urinary Catalase ($mm^3 O_2$/0.2 ml.)	Urinary Protein (mgm./100 ml.)
- 0.75	550	0
0	(tetrathionate injected)	
0.5	700	0
1.25	3400	30
17.0	470	15

Table 2

Catalasuria and Proteinuria in Rabbits

Rabbit #1A Sex - Male Weight - 2.7 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v.

Time (hrs.)	Urinary Catalase (mm^3O_2/0.2 ml.)	Urinary Protein (mgm./100 ml.)
- 0.25	45	0
0	(tetrathionate injected)	
1.0	23	0
2.0	23	0
3.0	107	0
4.0	214	0
5.0	507	5
6.0	2540	35

Table 3

Catalasuria and Proteinuria in Rabbits

Rabbit #5 Sex - Male Weight - 2.2 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v.

Time (hrs.)	Urinary Catalase (mm^3O_2/0.2 ml.)	Urinary Protein (mgm./100 ml.)
- 1.0	203	0
0	(tetrathionate injected)	
0.5	1670	10
1.5	12,400	400
3.0	35,000	300
4.5	14,700	300
5.5	4,240	200
6.5	1,750	150

Table 4

Catalasuria and Proteinuria in Rabbits

Rabbit #8 Sex - Female Weight - 2.5 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v.

Time (hrs.)	Urinary Catalase (mm^3O_2/0.2 ml.)	Urinary Protein (mgm./100 ml.)
- 0.5	384	0
0	(tetrathionate injected)	
0.5	237	0
1.0	57	0
2.0	85	0
3.0	68	0
4.0	90	0
5.0	102	0
6.5	260	trace
7.5	192	trace
26.0	950	0

Table 5

Catalasuria and Proteinuria in Rabbits

Rabbit #3 Sex - Male Weight - 2.7 kgm.

i.v. injections of $Na_2S_4O_6$ as indicated

Time (hrs.)	Urinary Catalase (mm^3O_2/0.2 ml.)	Urinary Protein (mgm./100 ml.)
- 2.5	766	0
0	(75 mgm./kgm. $S_4O_6^=$)	
1.0	3,280	30
2.0	9,150	400
3.0	17,000	500
4.0	10,200	400
5.0	4,400	400
6.0	4,400	400
71.5	510	0
72.0	(75 mgm./kgm. $S_4O_6^=$)	
72.5	266	trace
73.0	203	5
74.0	65	5
75.0	0	trace
76.0	0	trace
77.0	0	40
78.0	0	40
96.5	34.0	25
97.5	(100 mgm./kgm. $S_4O_6^=$)	
98.0	9.0	35
98.5	6.5	75
99.5	6.5	50
100.5	6.5	40
101.5	6.5	35
144.5	75.6	1000
145.5	47.5	1000
148.5	84.6	1000
148.75	(100 mgm./kgm. $S_4O_6^=$)	
149.25	57.5	1000
149.75	48.0	1000
169.0	82.5	1000
171.0	97.0	1000

Table 6

Summary of Clearance Experiments

Rabbit No.	$Na_2S_4O_6$ injected (mgm./ml.)	Clearance Times (hrs. after S_4O_6)	Clearances Done
65	100	0.5,1.0,2.0,3.0	In,PAH,Gl,Cl
64	100	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl
60	100	0.5,1.0,2.0,3.0,4.5	In,PAH,Gl
59	90	0.5,1.0,2.0,3.0	In,PAH
58	80	0.5,1.0,2.0,3.0	In,PAH
67	75	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl
66	75	0.5,1.0,2.0,3.0,3.5	In,PAH,Gl,Cl
57	70	0.5,1.0,2.0,3.0,4.0	In,PAH
56	60	0.5,1.0,1.5,2.0,3.0	In,PAH
71	50	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl
68	50	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl
53	50	0.5,1.0,1.5,2.0	In,PAH
55	35	0.5,1.0,1.5,2.0,3.0	In,PAH
75	25	0.5,1.0,2.0,4.0,5.0	In,PAH,Gl,Cl
73	25	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl
54	25	0.5,1.0,1.5,2.0	In,PAH
52	25	0.5,1.0,1.5,2.0,3.0	In,PAH
77	10	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl
76	10	0.5,1.0,2.0,3.0,4.0	In,PAH,Gl,Cl

Symbols In = inulin
PAH = para-aminohippurate
Gl = glucose
Cl = chlorides

Table 7

Clearance Studies in Rabbits

Analytical Data

Rabbit #65 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	1.0	0.31	2.04	1.02	21.2	1.10	0.08	6.70	6.80
- 0.25	1.1	0.32	2.18	1.14	22.4	1.14	0.08	6.40	6.90
0	-	-	-	-	-	-	-	-	-
0.5	0.09	0.52	2.48	2.24	13.8	1.36	0.90	6.77	6.65
1.0	0.21	0.66	1.38	2.76	7.40	1.36	1.04	6.85	7.10
2.0	0.53	0.81	1.15	3.84	5.44	1.08	1.60	6.65	6.90
3.0	0.84	1.04	1.36	4.50	5.68	1.00	1.46	6.93	6.95

Table 8

Clearance Studies in Rabbits

Calculated Data

Rabbit #65 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	5.8	21.0	16.3	0.07	0.08	6.30	0.99	1.01	6.80	32.0	0.85
- 0.25	6.5	21.0	17.8	0.08	0.08	7.40	0.99	1.10	7.40	34.2	0.84
0	-	-	-	-	-	-	-	-	-	-	-
0.5	0.43	0.56	0.4	0.006	0.08	0.51	0.86	0.09	0.60	2.31	0.79
1.0	0.44	0.56	0.5	0.16	0.22	0.38	0.63	0.22	1.49	1.53	0.50
2.0	0.75	0.75	0.5	0.78	0.85	-0.04	-0.04	0.55	3.66	1.33	0.27
3.0	1.1	1.1	0.7	1.22	1.21	-0.11	-0.12	0.84	5.84	1.78	0.23

Table 9

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #65 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2^{24}O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose			fgl	Chloride			fCl
				cleared	excreted	reabsorbed		cleared	excreted	reabsorbed	
- 0.5	(6.15)	(21.0)	(17.05)	(0.075)	(0.08)	(6.85)	(0.99)	(1.05)	(7.10)	(33.1)	(0.85)
- 0.25											
0	-	-	-	-	-	-	-	-	-	-	-
0.5	7.0	2.7	2.3	8	100	7.4	87	8.6	8.4	7.0	93
1.0	7.2	2.7	2.9	210	275	5.7	64	21	21	4.6	59
2.0	12.2	3.6	2.9	1040	1060	0	0	52	51.5	4.0	32
3.0	18.0	5.2	4.1	1630	1510	0	0	80	82.3	5.4	27

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values

Table 10

Clearance Studies in Rabbits

Analytical Data

Rabbit #64 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.25	0.11	4.81	0.33	55.6	1.52	1.10	6.75	5.80
- 0.25	0.25	0.17	5.24	0.41	56.4	1.80	0.84	6.40	6.85
0	-	-	-	-	-	-	-	-	-
0.5	0.03	*	1.31	*	6.80	1.74	0.80	*	4.25
1.0	0.01	0.37	2.44	1.60	14.0	1.54	0.80	6.45	*
2.0	0.39	0.48	0.54	2.20	2.90	1.48	2.26	6.40	6.60
3.0	0.40	0.59	0.58	2.78	3.30	1.42	2.20	6.40	6.75
4.0	0.33	0.60	0.70	3.28	3.86	1.36	2.06	6.55	6.70

* Sample lost

Table 11

Clearance Studies in Rabbits

Calculated Data

Rabbit #64 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	11.3	42.1	10.7	0.18	0.27	16.7	0.98	0.21	1.45	74.7	0.98
- 0.25	7.9	34.4	11.4	0.12	0.21	14.0	0.99	0.27	1.71	52.8	0.97
0	-	-	-	-	-	-	-	-	-	-	-
0.5	*	*	*	0.01	0.24	*	*	*	0.13	*	*
1.0	0.05	0.06	0.02	0.005	0.005	0.07	0.92	*	*	*	*
2.0	0.43	0.51	0.30	0.59	0.88	-0.25	-0.36	0.40	2.58	0.18	0.08
3.0	0.39	0.48	0.40	0.62	0.88	-0.33	-0.59	0.42	2.70	-0.20	-0.08
4.0	0.39	0.39	0.10	0.49	0.68	-0.16	-0.34	0.34	2.21	0.35	0.13

* Sample lost

Table 12

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #64 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5 - 0.25	(9.6)	(38.3)	(11.1)	(0.15)	(0.24)	(15.4)	(0.99)	(0.24)	(1.58)	(63.8)	(0.98)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	*	*	*	6.7	100	*	*	*	8.2	*	*
1.0	0.5	0.2	0.2	3.3	2.1	0.5	93	*	*	*	*
2.0	4.5	1.3	2.7	390	367	0	0	170	163	2.8	0.8
3.0	4.1	1.3	3.6	410	367	0	0	170	171	0	0
4.0	4.1	1.0	0.9	330	283	0	0	170	140	5.5	1.3

* Sample lost

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 13

Clearance Studies in Rabbits

Analytical Data

Rabbit #60 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.61	0.46	2.92	0.53	24.2	1.30	0.22
- 0.25	0.65	0.47	2.62	0.53	23.1	1.36	0.12
0	-	-	-	-	-	-	-
0.5	0.07	0.53	2.45	1.90	0.62	1.34	0.33
1	0.15	0.79	2.39	1.38	4.28	1.34	1.22
2	0.69	0.91	1.17	3.67	5.34	1.14	1.74
3	0.91	1.02	1.11	4.66	6.00	0.82	1.20
4.5	0.89	1.28	1.71	6.08	7.70	0.64	0.78

Table 14

Clearance Studies in Rabbits

Calculated Data

Rabbit #60 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl
- 0.5	3.9	28.3	13.1	0.10	0.12	4.94	0.97
- 0.25	3.7	28.6	13.5	0.06	0.08	4.95	0.98
0	-	-	-	-	-	-	-
0.5	0.32	0.02	-0.5	0.02	0.02	0.41	0.95
1	0.46	0.48	0.1	0.01	0.19	0.43	0.70
2	0.89	1.0	1.0	1.5	1.2	-0.17	-0.18
3	1.0	1.2	1.7	1.3	1.1	-0.28	-0.35
4.5	1.2	1.1	0.8	1.1	0.70	0.07	0.09

Table 15

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #60 Sex - Male Weight - 2.5 kgm.

100 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl
- 0.5 - 0.25	(3.8)	(28.5)	(13.3)	(0.08)	(0.10)	(4.95)	(0.98)
0	-	-	-	-	-	-	-
0.5	8.4	0.07	0	25	20	8.3	97
1	12	1.7	0.75	13	19	8.7	72
2	23	3.5	7.5	1880	1200	0	0
3	26	4.2	13	1620	1100	0	0
4.5	32	3.9	6.0	1380	700	1.4	9.2

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 17

Clearance Studies in Rabbits

Calculated Data

Rabbit #59 Sex - Male Weight - 2.5 kgm.

90 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 0.75	6.4	18.6	12.6
- 0.50	6.5	19.0	13.5
0	-	-	-
0.5	0.33	0.56	0.6
1	0.54	0.75	0.8
2	1.0	1.10	1.0
3	0.98	1.70	2.5

Table 18

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #59 Sex - Male Weight - 2.5 kgm.

90 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 0.75			
- 0.50	(6.45)	(18.8)	(13.1)
0	-	-	-
0.5	5.1	3.0	4.6
1	8.4	4.0	6.1
2	15	5.9	7.7
3	15	9.0	19

Figures in parentheses indicate mean control values.
All other figures denote per cent of mean control values.

Table 19

Clearance Studies in Rabbits

Analytical Data

Rabbit #58 Sex - Male Weight - 3.0 kgm.

80 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 0.75	0.40	0.23	5.71	0.63	41.5
- 0.50	0.32	0.28	7.26	0.63	54.5
0	0.32*	0.26*	7.85*	0.64*	61.5*
0.5	0.17	0.37	5.83	1.03	31.9
1	0.29	0.43	4.82	1.56	18.7
2	0.45	0.63	4.09	2.30	17.4
3	0.53	0.59	4.41	2.54	18.7

* clearance period coincided with tetrathionate injection.

Table 20

Clearance Studies in Rabbits

Calculated Data

Rabbit #58 Sex - Male Weight - 3.0 kgm.

80 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 0.75	9.8	26.6	11.6
- 0.50	8.3	27.9	13.1
0	9.6*	31.0*	14.2*
0.5	2.7	5.4	3.2
1	3.3	3.5	1.2
2	3.0	3.4	2.2
3	3.9	3.9	1.6

* clearance period coincided with tetrathionate injection.

Table 21

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #58 Sex - Male Weight - 2.5 kgm.

80 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 0.75	(6.45)	(28.5)	(13.1)
- 0.50			
0	*	*	*
0.5	29	19	25
1	36	12	9.3
2	33	12	17
3	42	14	12

* clearance period coincided with tetrathionate injection; data were included in calculation of mean control values.

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 22

Clearance Studies in Rabbits

Analytical Data

Rabbit #67 Sex - Male Weight - 2.5 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.36	0.36	1.83	1.09	17.8	2.56	0.56	6.07	4.70
- 0.25	0.36	0.38	1.84	1.10	18.0	2.65	0.48	6.53	4.38
0	-	-	-	-	-	-	-	-	-
0.5	0.16	0.46	1.30	1.54	6.24	2.50	1.46	6.27	6.40
1	0.16	0.51	1.15	1.86	4.40	2.56	2.92	6.87	6.77
2	0.29	0.63	1.04	2.18	3.70	2.45	3.88	6.35	6.50
3	0.26	0.70	1.15	2.69	4.15	2.47	3.96	7.00	6.77
4	0.21	0.66	1.21	2.94	4.80	2.56	3.80	6.40	6.20

Table 23

Clearance Studies in Rabbits

Calculated Data

Rabbit #67 Sex - Male Weight - 2.5 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	1.8	5.9	4.8	0.08	0.20	4.31	0.96	0.28	1.69	9.2	0.85
- 0.25	1.8	5.6	4.8	0.07	0.17	4.60	0.96	0.24	1.58	10.2	0.86
0	-	-	-	-	-	-	-	-	-	-	-
0.5	0.46	0.64	0.93	0.09	0.23	0.92	0.80	0.16	1.02	1.86	0.64
1	0.36	0.38	0.13	0.18	0.47	0.45	0.49	0.15	1.08	2.40	0.56
2	0.48	0.49	0.18	0.46	1.16	0.02	0.05	0.30	1.89	1.16	0.38
3	0.42	0.40	0.13	0.42	1.03	0.01	0.02	0.25	1.76	1.18	0.41
4	0.39	0.32	0.02	0.31	0.80	0.20	0.19	0.20	1.31	1.19	0.48

Table 24

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #67 Sex - Male Weight - 2.5 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose			fgl	Chloride			fCl
				cleared	excreted	reabsorbed		cleared	excreted	reabsorbed	
- 0.5											
- 0.25	(1.8)	(5.8)	(4.8)	(0.075)	(0.19)	(4.46)	(0.96)	(0.26)	(1.64)	(9.7)	(0.86)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	26	11	19	120	121	21	83	61	62	19	75
1	20	6.6	2.7	240	247	10	51	58	66	25	66
2	27	8.4	3.8	610	610	0.4	5.2	120	115	12	44
3	23	6.9	2.7	560	540	0.2	2.1	96	107	12	48
4	22	5.5	0.4	410	421	4.5	19	77	80	12	56

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 25

Clearance Studies in Rabbits

Analytical Data

Rabbit #66 Sex - Male Weight - 3.5 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.84	0.24	2.62	0.65	22.0	2.22	0.28	6.50	7.07
- 0.25	0.87	0.25	3.21	0.65	27.6	2.27	0.28	7.15	7.90
0	-	-	-	-	-	-	-	-	-
0.5	0.69	0.37	1.55	1.45	6.55	2.66	3.60	6.90	8.40
1	0.60	0.51	1.89	1.86	6.10	2.88	6.88	7.60	6.70
2	1.4	0.60	1.34	2.76	5.52	2.88	5.44	7.15	7.25
3	1.7	0.63	1.38	3.44	5.62	2.96	4.28	7.03	7.60
3.5	2.0	0.67	1.20	3.54	5.55	2.64	4.06	6.95	6.93

Table 26

Clearance Studies in Rabbits

Calculated Data

Rabbit #66 Sex - Male Weight - 3.5 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	9.1	28.7	13.6	0.11	0.24	20.0	0.99	0.91	5.94	53.2	0.90
- 0.25	11.3	37.0	17.9	0.10	0.24	25.4	0.99	0.96	6.88	73.7	0.92
0	-	-	-	-	-	-	-	-	-	-	-
0.5	2.9	3.1	1.0	0.93	2.48	5.24	0.68	0.83	5.80	14.2	0.71
1	2.2	2.0	0.3	1.43	4.13	2.21	0.36	0.52	4.02	12.7	0.76
2	3.1	2.8	0.5	2.60	7.61	1.32	0.16	1.40	10.1	12.1	0.55
3	3.7	2.8	-0.5	2.8	7.27	3.73	0.34	1.80	12.9	13.1	0.51
3.5	3.6	3.1	0.6	3.1	8.12	1.38	0.14	1.90	13.9	11.1	0.44

Table 27

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #66 Sex - Male Weight - 3.5 kgm.

75 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5 - 0.25	(10.2)	(32.9)	(15.8)	(0.11)	(0.24)	(22.7)	(0.99)	(0.94)	(6.41)	(63.5)	(0.91)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	28	9.4	6.4	890	1030	23.0	69	89	90	22	78
1	21	6.1	1.9	1360	1720	9.7	36	56	63	20	84
2	30	8.5	3.2	2480	3170	5.8	16	150	157	19	60
3	36	8.5	0	2670	3030	16.4	34	190	201	21	56
3.5	35	9.4	3.8	2950	3380	6.1	14	200	217	17	48

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 28

Clearance Studies in Rabbits

Analytical Data

Rabbit #57 Sex - Male Weight - 2.5 kgm.

70 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 0.50	0.28	0.70	4.02	2.17	31.4
- 0.25	0.42	0.69	4.74	2.17	31.4
0	0.39*	0.71*	3.94*	2.35*	30.6*
0.5	0.25	0.98	3.31	2.89	20.0
1	0.15	1.11	3.65	3.63	20.0
2	0.13	1.32	3.22	4.84	21.0
3	0.35	1.32	3.94	5.54	18.9
4	0.12	1.57	5.05	6.49	23.0

* clearance period coincided with tetrathionate injection.

Table 29

Clearance Studies in Rabbits

Calculated Data

Rabbit #57 Sex - Male Weight - 2.5 kgm.

70 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 0.5	1.6	4.1	5.9
- 0.25	2.9	6.2	8.1
0	2.2*	5.0*	7.6*
0.5	0.86	1.8	3.0
1	0.48	0.81	1.5
2	0.32	0.58	1.5
3	1.0	1.2	1.9
4	0.39	0.43	0.70

* clearance period coincided with tetrathionate injection.

Table 30

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #57 Sex - Male Weight - 2.5 kgm.

70 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 0.5			
- 0.25	(2.23)	(5.1)	(7.2)
0	*	*	*
0.5	39	35	42
1	22	16	21
2	14	11	21
3	45	24	26
4	17	8.4	9.7

* clearance period coincided with tetrathionate injection; data were included in calculation of mean control values.

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 31

Clearance Studies in Rabbits

Analytical Data

Rabbit #56 Sex - Male Weight - 2.7 kgm.

60 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 0.75	0.61	0.27	4.43	0.93	30.6
- 0.50	0.65	0.29	3.41	0.93	23.8
0	-	-	-	-	-
0.5	0.07	0.39	1.75	1.48	9.5
1	0.15	0.49	1.73	1.98	7.8
1.5	0.69	0.50	2.25	2.36	9.8
2	0.91	0.52	3.11	2.56	14.3
3	0.89	0.52	3.31	3.08	17.8

Table 32

Clearance Studies in Rabbits

Calculated Data

Rabbit #56 Sex - Male Weight - 2.7 kgm.

60 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 0.75	8.8	18.1	9.9
- 0.50	10.0	21.7	12.5
0	-	-	-
0.5	2.1	3.0	1.8
1	3.0	3.3	1.6
1.5	3.5	3.3	0.9
2	3.2	3.0	0.9
3	3.1	2.8	0.9

Table 33

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #56 Sex - Male Weight - 2.7 kgm.

60 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 0.75 - 0.50	(9.4)	(19.9)	(11.2)
0	-	-	-
0.5	22	15	16
1	32	17	14
1.5	37	17	8
2	34	15	8
3	33	14	8

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 34

Clearance Studies in Rabbits

Analytical Data

Rabbit #71 Sex - Male Weight - 2.9 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.35	0.23	2.61	0.34	32.2	2.60	0.56	6.85	1.90
- 0.25	0.30	0.26	2.71	0.38	30.2	2.54	0.48	6.55	2.45
0	-	-	-	-	-	-	-	-	-
0.5	0.12	0.32	2.00	0.80	22.9	2.47	0.34	7.45	1.80
1	0.06	0.35	1.37	1.06	9.72	2.17	0.60	7.15	4.60
2	0.55	0.38	2.03	1.40	9.84	1.54	2.32	7.20	5,60
3	0.69	0.33	1.69	1.78	9.10	1.14	1.74	6.95	6.75
4	0.63	0.36	1.79	1.86	9.50	1.18	1.80	6.95	6.65

Table 35

Clearance Studies in Rabbits

Calculated Data

Rabbit #71 Sex - Male Weight - 2.9 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	3.6	32.8	10.3	0.08	0.20	9.16	0.98	0.10	0.67	23.9	0.98
- 0.25	3.1	23.7	8.1	0.06	0.14	7.72	0.98	0.11	0.74	19.7	0.96
0	-	-	-	-	-	-	-	-	-	-	-
0.5	0.75	3.4	2.2	0.02	0.04	1.80	0.98	0.03	0.22	5.37	0.96
1	0.23	0.54	0.38	0.02	0.36	0.14	0.93	0.04	0.28	1.36	0.84
2	2.9	3.8	1.9	0.83	1.28	3.19	0.72	0.42	3.08	17.8	0.86
3	3.4	3.5	1.2	1.1	1.20	2.68	0.70	0.67	4.66	18.9	0.81
4	3.1	3.2	1.1	0.96	1.13	2.53	0.70	0.60	4.19	17.4	0.81

Table 36

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #71 Sex - Male Weight - 2.9 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5 - 0.25	(3.35)	(28.3)	(9.2)	(0.07)	(0.17)	(8.44)	(0.98)	(0.11)	(0.71)	(21.8)	(0.97)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	22	12	24	29	23	21	100	29	31	25	99
1	6.9	1.9	4.1	29	210	1.7	95	38	39	6.2	87
2	86	13	21	1190	750	38	74	400	430	82	89
3	101	12	13	1570	710	32	71	640	660	87	83
4	93	11	12	1370	670	30	71	580	590	80	83

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 37

Clearance Studies in Rabbits

Analytical Data

Rabbit #68 Sex - Male Weight - 2.5 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	1.80	0.44	0.81	2.00	7.20	2.52	0.98	7.03	6.70
- 0.25	1.73	0.41	0.77	2.00	8.60	2.64	0.90	7.53	6.73
0	-	-	-	-	-	-	-	-	-
0.5	0.48	0.47	0.89	2.58	5.65	2.76	2.72	7.25	7.92
1	1.16	0.56	1.67	2.94	5.00	2.32	3.84	7.92	7.10
2	1.06	0.64	1.00	3.56	6.25	1.60	2.94	7.75	7.30
3	1.11	0.64	1.08	4.00	7.35	1.00	2.00	7.95	7.42
4	1.10	0.70	1.39	4.32	8.16	0.80	1.54	7.95	7.50

Table 38

Clearance Studies in Rabbits

Calculated Data

Rabbit #68 Sex - Male Weight - 2.5 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.50	3.3	6.5	7.4	0.70	1.77	6.55	0.79	1.7	12.1	11.1	0.49
- 0.25	3.2	7.3	9.3	0.60	1.56	6.89	0.82	1.5	11.7	12.4	0.53
0	-	-	-	-	-	-	-	-	-	-	-
0.5	0.9	1.1	1.4	0.47	1.30	1.18	0.48	0.52	3.80	2.73	0.43
1	3.6	2.0	-2.9	1.9	4.46	3.89	0.45	1.1	8.25	20.2	0.70
2	1.7	1.9	1.8	2.0	3.12	-0.40	-0.18	1.0	7.75	5.45	0.40
3	1.8	2.0	2.1	2.2	2.22	-0.42	-0.18	1.0	8.24	6.06	0.45
4	2.2	2.1	1.5	2.1	1.70	0.06	0.03	1.0	8.25	9.25	0.52

Table 39

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #68 Sex - Male Weight - 2.5 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose			fgl	Chloride			fCl
				cleared	excreted	reabsorbed		cleared	excreted	reabsorbed	
- 0.5											
- 0.25	(3.25)	(6.9)	(8.35)	(0.65)	(1.67)	(6.72)	(0.81)	(1.6)	(11.9)	(11.8)	(0.51)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	28	16	17	72	78	18	60	32	32	23	84
1	110	29	0	290	270	58	56	69	69	170	137
2	52	28	22	310	190	0	0	63	65	46	78
3	55	29	25	340	130	0	0	63	69	51	88
4	68	30	18	320	100	4	4	63	69	78	102

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 40

Clearance Studies in Rabbits

Analytical Data

Rabbit #53 Sex - Male Weight - 2.5 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 0.50	0.45	0.29	5.75	0.64	41.0
- 0.25	0.42	0.27	6.05	0.71	44.8
0	-	-	-	-	-
0.5	0.30	0.27	5.95	0.72	34.6
1	0.39	0.30	5.47	0.99	25.4
1.5	0.37	0.33	5.37	1.09	27.0
2	0.34	0.36	6.63	1.25	34.8

Table 41

Clearance Studies in Rabbits

Calculated Data

Rabbit #53 Sex - Male Weight - 2.5 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 0.50	9.1	29.0	13.8
- 0.25	9.3	26.5	13.1
0	-	-	-
0.5	6.7	14.5	6.4
1	7.0	10.0	4.1
1.5	6.0	9.2	4.6
2	6.2	9.5	5.3

Table 42

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #53 Sex - Male Weight - 2.5 kgm.

50 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 0.5 - 0.25	(9.2)	(27.8)	(13.5)
0	-	-	-
0.5	73	52	48
1	76	36	30
1.5	65	33	34
2	67	34	39

Figures in parentheses indicate mean control values.
All other figures denote per cent of mean control values.

Table 43

Clearance Studies in Rabbits

Analytical Data

Rabbit #55 Sex - Male Weight - 2.1 kgm.

35 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 1.2	0.32	0.27	5.79	0.71	56.4
- 0.7	0.40	0.29	5.60	0.69	52.0
0	-	-	-	-	-
0.5	0.21	0.32	3.14	1.07	23.4
1	0.61	0.29	1.79	1.22	9.2
1.5	0.59	0.33	1.94	1.52	11.6
2	0.63	0.36	1.79	1.69	11.8
3	0.53	0.40	2.14	2.16	15.2

Table 44

Clearance Studies in Rabbits

Calculated Data

Rabbit #55 Sex - Male Weight - 2.1 kgm.

35 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 1.2	6.8	25.6	14.1
- 0.7	7.8	30.4	16.4
0	-	-	-
0.5	2.0	4.5	3.0
1	3.8	4.6	1.8
1.5	3.5	4.6	1.6
2	3.1	4.4	3.0
3	2.8	3.8	3.0

Table 45

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #55 Sex - Male Weight - 2.1 kgm.

35 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 1.2 - 0.7	(7.3)	(28.0)	(15.3)
0	-	-	-
0.5	27	16	20
1	52	16	12
1.5	48	16	10
2	42	16	20
3	38	14	20

Figures in parentheses indicate mean control values.
All other figures denote per cent of mean control values.

Table 46

Clearance Studies in Rabbits

Analytical Data

Rabbit #75 Sex - Female Weight - 2.6 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.39	0.23	3.76	0.36	34.6	1.60	0.32	1.44	2.06
- 0.25	0.32	0.21	4.48	0.35	33.4	1.76	0.36	1.43	2.38
0	-	-	-	-	-	-	-	-	-
0.5	0.24	0.12	5.66	0.20	46.8	1.80	0.42	1.50	1.56
1	0.25	0.27	6.22	0.54	41.6	1.85	4.88	1.50	0.94
2	0.29	0.25	5.60	0.59	38.0	1.88	7.44	1.49	1.30
4	0.25	0.19	5.60	0.55	46.8	1.80	6.84	1.54	1.40
5	0.20	0.17	6.66	0.52	58.4	1.80	6.84	1.54	1.24

Table 47

Clearance Studies in Rabbits

Calculated Data

Rabbit #75 Sex - Female Weight - 2.6 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	6.5	37.2	11.6	0.08	0.13	10.3	0.99	0.55	0.80	8.55	0.91
- 0.25	6.9	30.9	8.7	0.07	0.12	12.0	0.99	0.53	0.76	9.12	0.92
0	-	-	-	-	-	-	-	-	-	-	-
0.5	11.5	56.0	9.4	0.06	0.10	20.6	0.99	0.25	0.37	16.9	0.98
1	5.9	19.3	7.8	0.65	1.22	9.7	0.89	0.15	0.33	8.52	0.97
2	6.6	18.6	7.9	1.10	2.16	10.2	0.83	0.25	0.38	9.46	0.96
4	7.5	21.1	8.4	0.95	1.71	11.8	0.87	0.22	0.35	11.2	0.97
5	7.8	22.6	8.4	0.76	1.37	12.7	0.90	0.16	0.25	11.7	0.98

Table 48

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #75 Sex - Female Weight - 2.6 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5											
- 0.25	(6.7)	(34.1)	(10.2)	(0.08)	(0.13)	(11.2)	(0.99)	(0.54)	(0.78)	(8.84)	(0.92)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	172	164	93	80	77	184	100	46	47	191	107
1	88	57	77	870	940	87	90	28	42	96	106
2	99	55	78	1470	1660	91	84	46	49	107	105
4	112	62	83	1270	1320	105	88	41	45	127	106
5	116	66	83	1010	1050	113	91	30	32	132	107

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 49

Clearance Studies in Rabbits

Analytical Data

Rabbit #73 Sex - Male Weight - 2.5 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.59	0.36	2.31	1.70	21.2	1.88	0.72	7.30	6.90
- 0.25	0.52	0.34	2.92	1.70	25.0	2.10	0.90	6.90	7.38
0	-	-	-	-	-	-	-	-	-
0.5	0.41	0.42	2.92	1.86	24.0	2.30	2.32	7.85	6.57
1	0.39	0.46	4.09	1.92	27.6	2.20	2.74	7.15	6.35
2	0.30	0.52	4.29	2.18	28.0	1.78	2.52	7.15	7.57
3	0.43	0.55	3.89	2.52	24.2	1.46	2.58	7.38	6.90
4	0.45	0.64	2.29	2.82	20.2	1.08	1.78	7.38	7.70

Table 50

Clearance Studies in Rabbits

Calculated Data

Rabbit #73 Sex - Male Weight - 2.5 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	3.8	7.4	7.1	0.23	0.42	6.73	0.94	0.56	4.06	3.18	0.85
- 0.25	4.4	7.6	6.8	0.22	0.47	8.78	0.95	0.56	3.84	4.06	0.87
0	-	-	-	-	-	-	-	-	-	-	-
0.5	2.8	5.3	5.4	0.41	0.95	5.50	0.85	0.34	2.70	3.07	0.88
1	3.4	5.6	5.4	0.49	1.07	6.41	0.86	0.35	2.48	3.86	0.90
2	2.5	3.8	3.8	0.42	0.76	3.69	0.83	0.32	2.27	2.38	0.87
3	3.0	4.1	4.2	0.62	1.11	3.27	0.75	0.39	2.96	2.80	0.87
4	1.6	3.2	5.4	0.74	0.81	0.92	0.54	0.46	3.46	-0.39	0.71

Table 51

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #73 Sex - Male Weight - 2.5 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5 - 0.25	(4.1)	(7.5)	(6.95)	(0.23)	(0.45)	(7.76)	(0.95)	(0.56)	(3.95)	(3.62)	(0.86)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	68	71	78	180	211	71	90	61	68	85	102
1	83	75	78	220	238	83	91	63	63	107	105
2	61	51	55	190	169	48	88	57	57	66	101
3	73	55	60	280	247	42	79	70	75	77	101
4	39	43	78	330	180	12	57	82	88	0	83

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 52

Clearance Studies in Rabbits

Analytical Data

Rabbit #54 Sex - Male Weight - 2.7 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 1.4	0.43	0.20	3.75	0.41	31.8
- 0.9	1.3	0.23	1.99	0.43	6.2
0	-	-	-	-	-
0.5	0.43	0.23	4.61	0.40	28.4
1	0.43	0.25	5.54	0.48	37.0
1.5	0.35	0.26	6.16	1.08	31.4
2	0.30	0.26	5.86	1.62	47.8

Table 53

Clearance Studies in Rabbits

Calculated Data

Rabbit #54 Sex - Male Weight - 2.7 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 1.4	8.1	33.4	11.0
- 0.9	11.2	18.8	4.1
0	-	-	-
0.5	8.5	30.5	9.4
1	9.5	15.9	12.1
1.5	8.4	10.2	3.5
2	6.8	8.9	5.2

Table 54

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #54 Sex - Male Weight - 2.7 kgm.

25 mgm./kgm. $Na_2S_4O_6$ I.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TSH
- 1.4 - 0.9	(9.65)	(26.1)	(8.55)
0	-	-	-
0.5	88	121	110
1	98	61	141
1.5	87	39	41
2	71	34	61

Figures in parentheses indicate mean control values.
All other figures denote per cent of mean control values.

Table 55

Clearance Studies in Rabbits

Analytical Data

Rabbit #52 Sex - Male Weight - 2.3 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)	
		Plasma	Urine	Plasma	Urine
- 0.50	0.31	0.20	7.86	0.55	62.5
- 0.25	0.34	0.20	7.24	0.48	64.5
0	-	-	-	-	-
0.5	0.40	0.20	6.74	0.48	44.5
1	0.49	0.20	5.44	0.44	37.5
1.5	0.45	0.19	5.16	0.53	37.5
2	0.43	0.19	5.68	0.47	51.3
3	0.50	0.20	5.50	0.50	42.5

Table 56

Clearance Studies in Rabbits

Calculated Data

Rabbit #52 Sex - Male Weight - 2.3 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)
- 0.5	12.3	36.0	14.0
- 0.25	12.3	46.2	17.1
0	-	-	-
0.5	13.5	37.5	12.5
1	13.4	41.3	13.3
1.5	12.0	32.3	11.8
2	13.2	47.1	17.0
3	13.9	42.5	15.5

Table 57

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #52 Sex - Male Weight - 2.3 kgm.

25 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM
- 0.5 - 0.25	(12.3)	(41.1)	(15.6)
0	-	-	-
0.5	110	91	80
1	109	100	86
1.5	98	79	76
2	107	114	109
3	113	103	100

Figures in parentheses indicate mean control values.
All other figures denote per cent of mean control values.

Table 58

Clearance Studies in Rabbits

Analytical Data

Rabbit #77 Sex - Male Weight - 2.8 kgm.

10 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow (ml./min.)	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
		Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.29	0.33	5.18	0.61	37.2	1.46	0.64	6.20	4.88
- 0.25	0.23	0.31	6.34	0.51	45.0	1.44	0.74	5.43	3.30
0	-	-	-	-	-	-	-	-	-
0.5	0.25	0.32	7.75	0.51	46.8	1.46	0.70	5.92	4.35
1	0.24	0.30	7.50	0.52	45.0	1.68	0.70	7.87	6.00
2	0.33	0.34	5.80	0.56	29.4	1.54	0.66	5.40	9.60
3	0.41	0.40	6.00	0.77	38.0	1.38	0.44	6.35	8.60
4	0.39	0.44	6.00	1.04	28.6	1.31	0.30	8.52	6.85

Table 59

Clearance Studies in Rabbits

Calculated Data

Rabbit #77 Sex - Male Weight - 2.8 kgm.

10 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	4.7	18.3	9.0	0.13	0.19	6.68	0.97	0.23	1.42	27.8	0.95
- 0.25	4.7	20.3	8.5	0.12	0.17	6.61	0.98	0.14	0.76	24.7	0.97
0	-	-	-	-	-	-	-	-	-	-	-
0.5	6.1	23.0	9.2	0.12	0.18	8.72	0.98	0.18	1.09	35.0	0.97
1	6.0	20.8	8.0	0.10	0.17	9.84	0.98	0.18	1.44	45.8	0.97
2	5.7	17.3	7.1	0.14	0.16	8.63	0.98	0.59	3.17	27.6	0.90
3	6.0	20.0	11.5	0.11	0.18	8.10	0.98	0.56	3.52	34.6	0.91
4	5.3	11.0	7.1	0.09	0.12	6.83	0.98	0.32	2.68	42.4	0.94

Table 60

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #77 Sex - Male Weight - 2.8 kgm.

10 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5 - 0.25	(0.47)	(19.3)	(8.75)	(0.13)	(0.18)	(6.65)	(0.98)	(0.19)	(1.09)	(26.3)	(0.96)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	130	119	105	96	100	131	100	97	100	133	101
1	128	108	91	80	94	148	100	97	132	174	101
2	121	90	81	110	89	130	100	320	291	105	94
3	128	104	131	88	100	122	100	300	323	132	95
4	113	57	81	72	67	103	100	170	246	161	98

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

Table 61

Clearance Studies in Rabbits

Analytical Data

Rabbit #76 Sex - Male Weight - 2.6 kgm.

10 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	Urine Flow	Inulin (mgm./ml.)		PAH (mgm./ml.)		Glucose (mgm./ml.)		Chloride (mgm./ml.)	
	(ml./min.)	Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine
- 0.5	0.66	0.40	3.34	1.30	9.40	3.10	0.92	1.48	1.48
- 0.25	0.54	0.46	4.30	1.35	12.6	3.24	0.73	1.75	1.27
0	-	-	-	-	-	-	-	-	-
0.5	0.34	0.46	5.88	1.41	17.6	2.94	0.61	0.66	1.04
1	0.27	0.49	6.02	1.44	16.6	2.67	0.40	1.40	1.51
2	0.20	0.47	6.25	1.44	31.4	1.98	0.54	1.54	0.91
3	0.22	0.49	4.85	1.46	24.0	1.52	0.32	1.79	1.16
4	0.15	0.46	7.92	1.36	39.6	1.44	0.58	1.59	0.48

Table 62

Clearance Studies in Rabbits

Calculated Data

Rabbit #76 Sex - Male Weight - 2.6 kgm.

10 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR (ml./min.)	PAH cleared (ml./min.)	TEM (mgm./min.)	Glucose cleared (ml./min.)	Glucose excreted (mgm./min.)	Glucose reabsorbed (mgm./min.)	fgl	Chloride cleared (ml./min.)	Chloride excreted (mgm./min.)	Chloride reabsorbed (mgm./min.)	fCl
- 0.5	5.5	4.8	0.4	0.20	0.61	16.5	0.96	0.66	0.98	7.17	0.88
- 0.25	5.1	5.0	1.0	0.12	0.39	16.1	0.98	0.39	0.69	8.24	0.92
0	-	-	-	-	-	-	-	-	-	-	-
0.5	4.4	4.2	1.0	0.07	0.21	12.7	0.98	0.54	0.35	2.55	0.88
1	3.3	3.1	0.8	0.04	0.11	8.70	0.99	0.29	0.41	3.92	0.91
2	2.6	4.3	3.4	0.05	0.11	5.04	0.98	0.11	0.18	3.82	0.95
3	2.2	3.6	2.2	0.05	0.71	2.64	0.98	0.14	0.26	3.68	0.93
4	2.6	4.3	3.2	0.06	0.87	2.87	0.98	0.05	0.07	4.07	0.98

Table 63

Clearance Studies in Rabbits

Calculated Data in Terms of Per Cent of Mean Control Values

Rabbit #76 Sex - Male Weight - 2.6 kgm.

10 mgm./kgm. $Na_2S_4O_6$ i.v. at 0 hrs.

Time (hrs.)	GFR	PAH cleared	TEM	Glucose cleared	Glucose excreted	Glucose reabsorbed	fgl	Chloride cleared	Chloride excreted	Chloride reabsorbed	fCl
- 0.5											
- 0.25	(5.3)	(4.9)	(0.70)	(0.16)	(0.50)	(16.3)	(0.97)	(0.53)	(0.84)	(7.71)	(0.90)
0	-	-	-	-	-	-	-	-	-	-	-
0.5	83	86	140	44	42	78	101	102	42	33	98
1	62	63	114	25	22	53	102	55	49	51	101
2	49	88	490	31	22	31	101	21	21	50	105
3	42	74	315	31	142	16	101	26	31	48	103
4	49	88	460	37	174	18	101	9	8	53	109

Figures in parentheses indicate mean control values. All other figures denote per cent of mean control values.

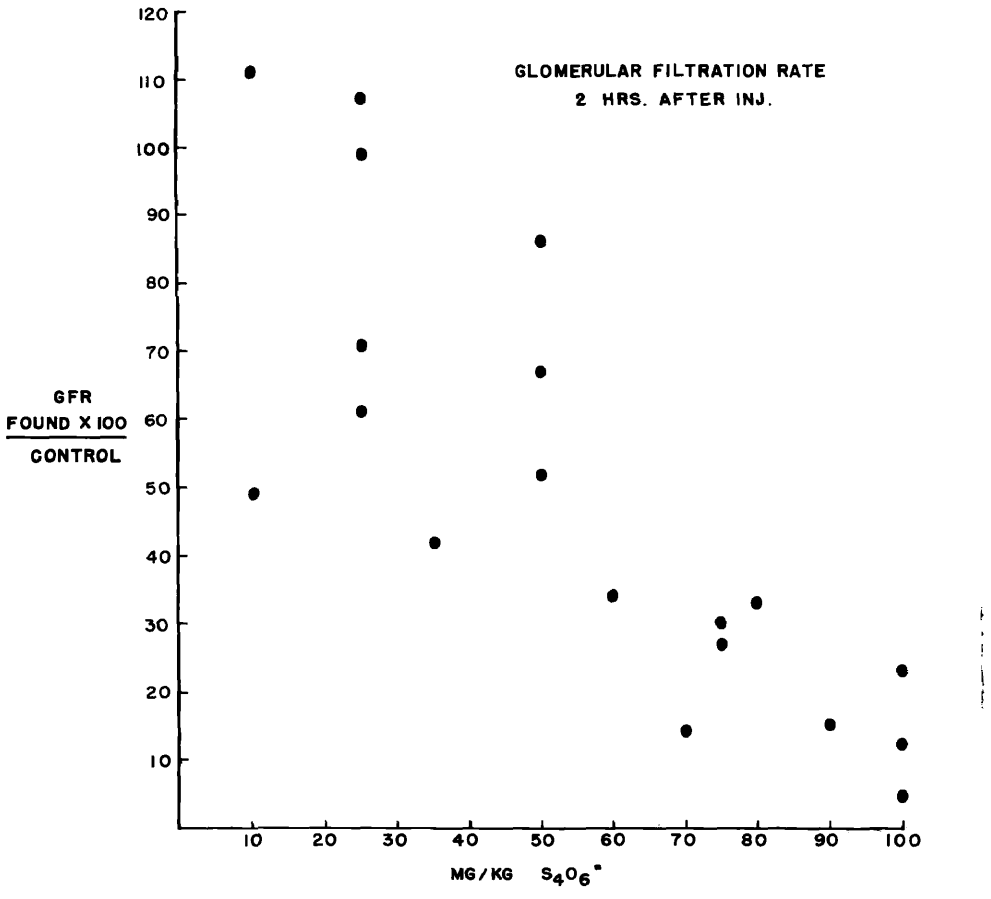

Figure 1

Glomerular filtration rate (inulin clearance) for various doses of tetrathionate.

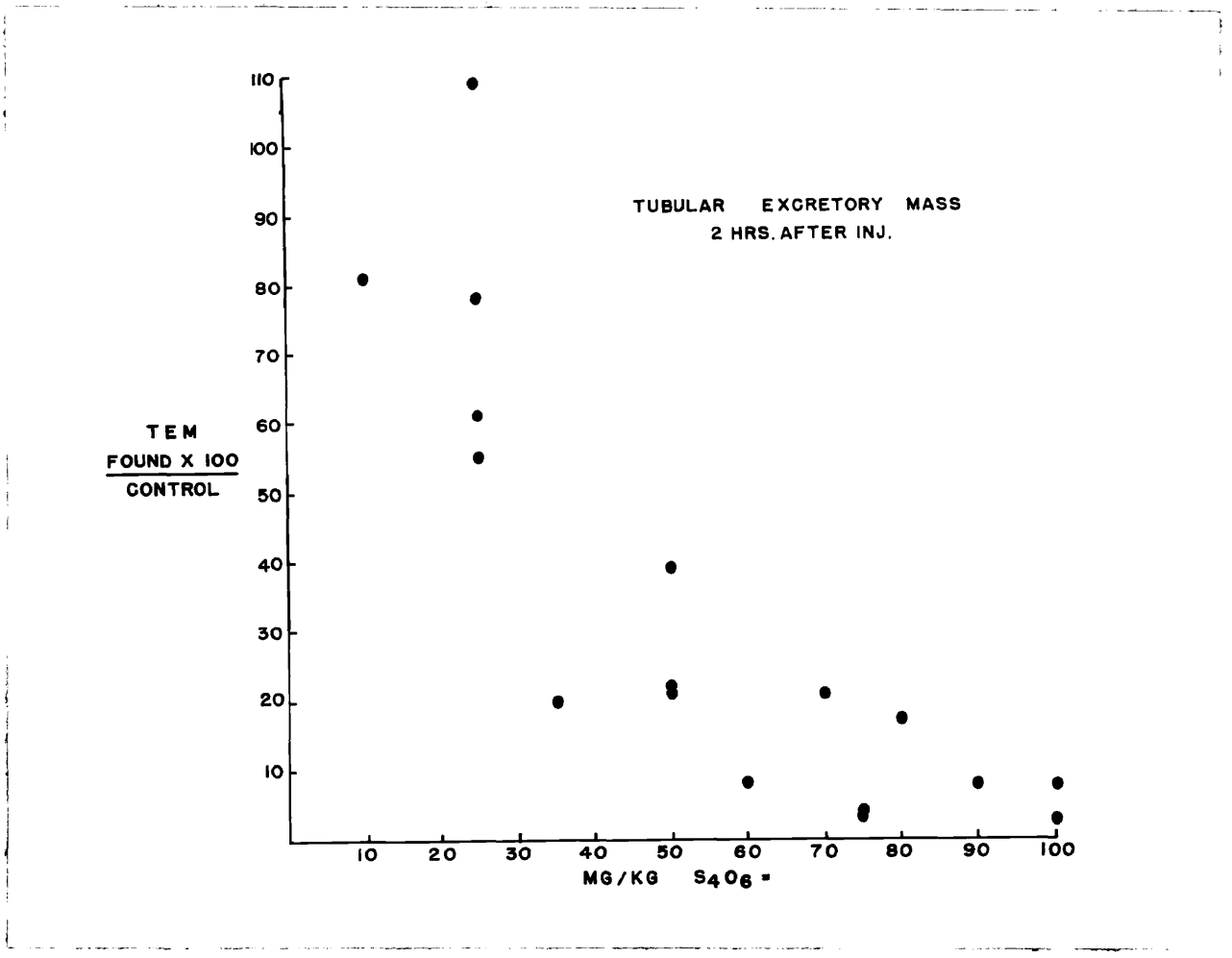

Figure 2

Tubular excretory mass (para-aminohippurate) for various doses of tetrathionate.

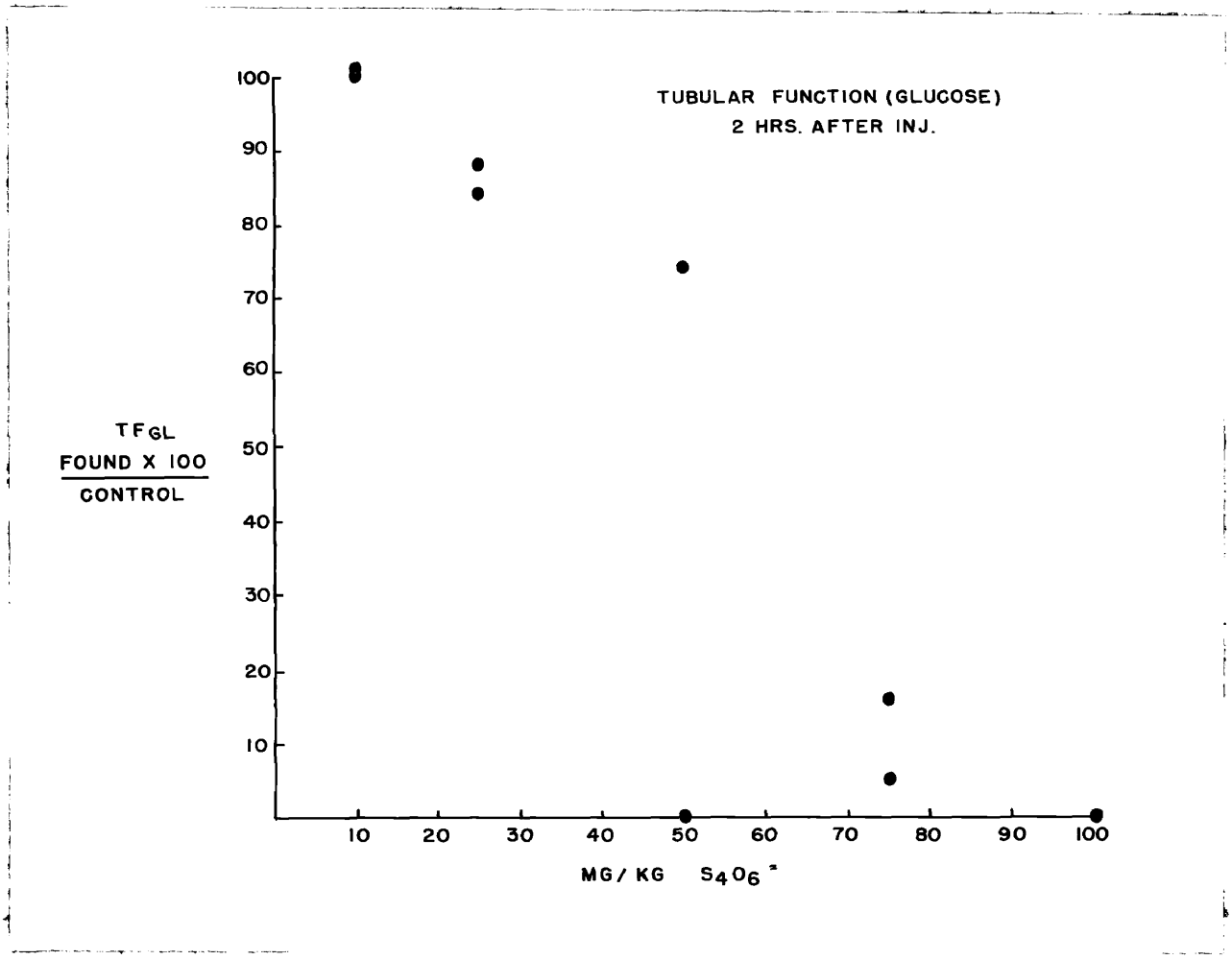

Figure 3

Tubular transport of glucose for various doses of tetrathionate.

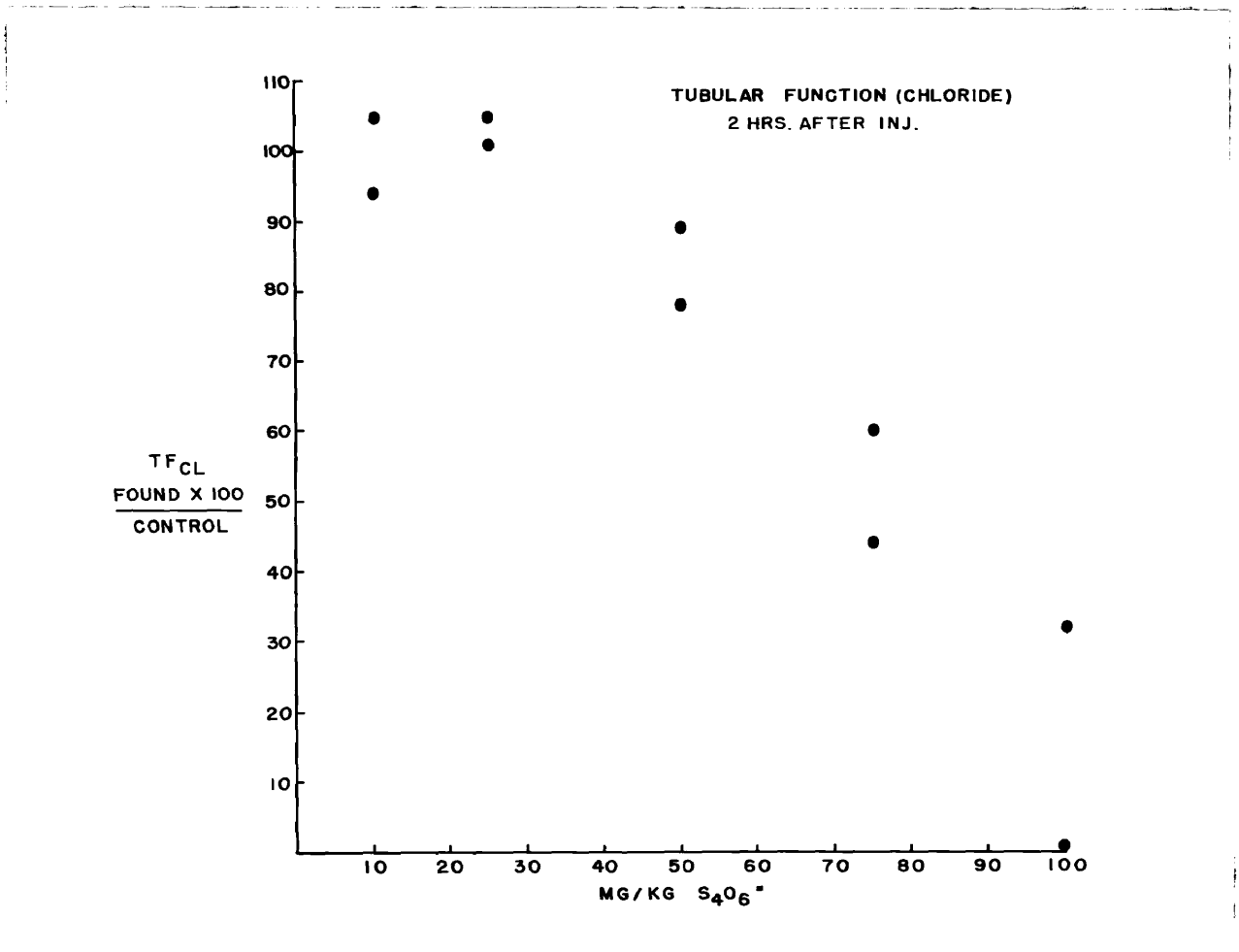

Figure 4

Tubular transport of chloride for various doses of tetrathionate.

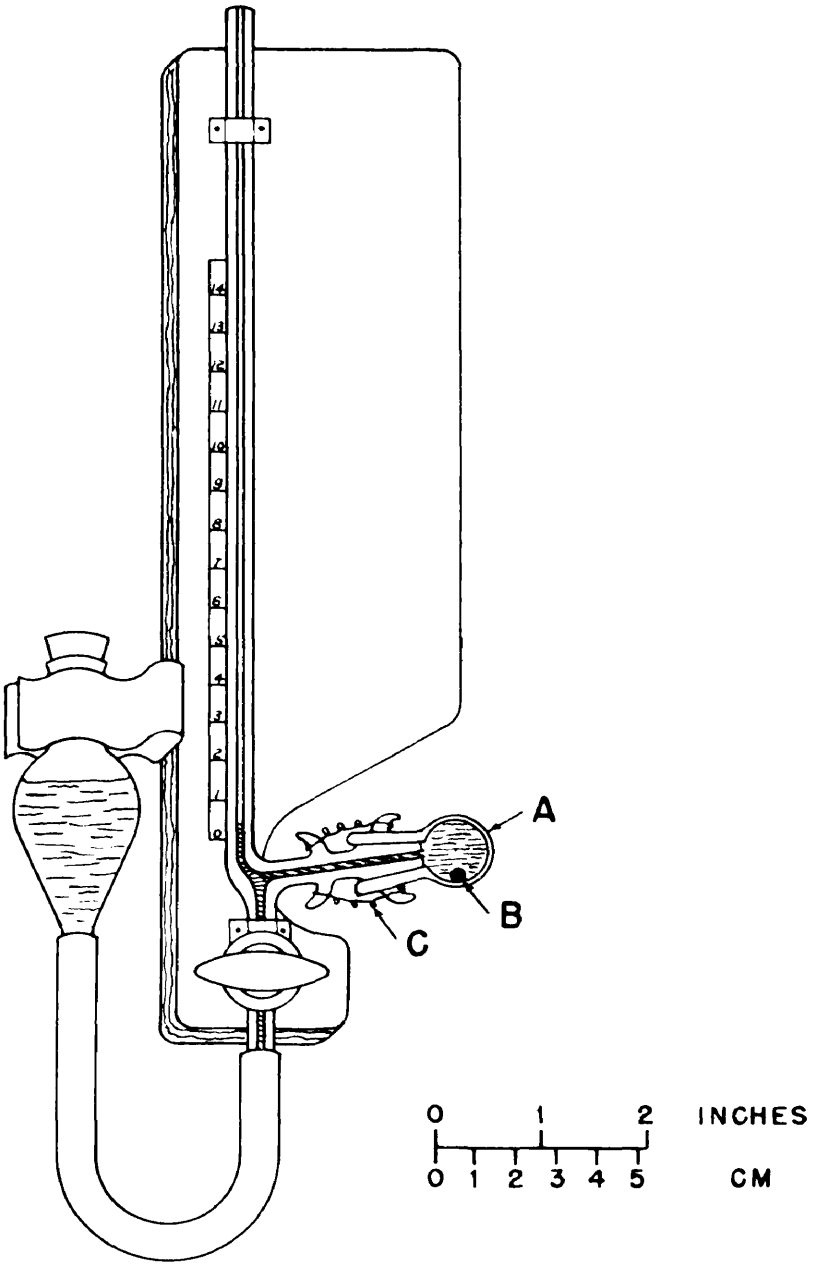

Figure 5

Manometer assembly of the Bounce apparatus. The manometer, made of capillary tubing with a 1-mm bore, is mounted on a wooden block 3/4 in. thick. The bulb A contains just 1.5 ml of liquid when filled to the neck without the glass bead B. The bulb is fastened to the manometer by spring C (or by means of a thin section of rubber tubing).

APPENDIX B

Chemistry of sodium tetrathionate. Pure samples of sodium tetrathionate ($Na_2S_4O_6 \cdot 2H_2O$) were prepared by the dropwise addition of a concentrated solution of $Na_2S_2O_3 \cdot 5H_2O$ (250 grams in 150 ml. H_2O) to an alcoholic solution of iodine (127 grams I_2 and 50 grams NaI in 500 ml. of 90 per cent ethanol)(58). The reaction mixture was stirred vigorously and maintained below 20° C during the addition of thiosulfate. Completion of the reaction was indicated when the color of the iodine solution attained a straw-like hue. One liter of absolute ethanol and 500 ml. of anhydrous ethyl ether were then added to the reaction mixture. After precipitation appeared complete, the tetrathionate was collected on a Buchner funnel and washed with small portions of absolute ethanol in order to remove excess iodine. The precipitate was then air-dried with suction and dissolved in an equal weight of water. The solution was filtered and the filtrate allowed to fall directly into 1 liter of absolute ethanol. The precipitate so formed was collected on a Buchner funnel, washed well with absolute ethanol, and dried at room temperature to constant weight in vacuo over calcium chloride. The yield was about 100 grams of white, crystalline material which was readily soluble in an equal weight of water to form a clear solution with no iodine uptake. Sodium tetrathionate crystallizes out of ethanol-water as the hydrated salt, $Na_2S_4O_6 \cdot 2H_2O$ (59). The compound prepared by this procedure also appears to contain two molecules of water since on cautious drying at 80° C, a 11.4 to 11.8 per cent weight loss occurs (28). The theoretical value for the loss of two molecules of water is 11.8 per cent.

The tetrathionate content of the hydrated salt may be determined by the reaction of the tetrathionate ion with cyanide (60, 61), which is dependent upon the following reaction:

$$S_4O_6^{=} + CN^{-} + H_2O \rightarrow S_2O_3^{=} + CNS^{-} + SO_4^{=} + 2H^{+}$$

In this reaction, one mol. of thiosulfate is quantitatively formed from each mol of tetrathionate and the uptake of iodine by the reaction product provides a direct measure of the original content of tetrathionate. The sample of tetrathionate used in this study was found to analyze by the cyanide procedure as 100.4 per cent of $Na_2S_4O_6 \cdot 2H_2O$.

APPENDIX C

The determination of catalase in urine. Catalase reacts with H_2O_2 to form catalase peroxide and water. The catalase peroxide then reacts with a second molecule of H_2O_2 to form regenerated catalase, water, and molecular oxygen. The reaction can be pictured according to the following scheme (62):

$$Cat + 2H_2O_2 \rightarrow Cat\langle{}^{O}_{O} + 2H_2O$$

$$2Cat\langle{}^{O}_{O} + 2H_2O_2 \rightarrow 2Cat + 2H_2O + 3O_2$$

Accordingly, any manometric method which determines the rate of oxygen production in this reaction would give an estimate of the amount of catalase activity of a given sample. Two manometric methods are available for this purpose; the Warburg apparatus for measuring gas production (63), and the manometric apparatus devised by Dounce (47). The advantage of the Dounce apparatus over that of Warburg is that the former is more compact and portable, and requires less time for an analysis.

The essential parts of the Dounce apparatus are the manometer and bulb assembly (figure 5), and some device for oscillating the manometer assembly about a horizontal axis at its upper end at a rate of about 250 oscillations per minute (47).

A clean glass bead is placed in the bottom of the bulb, and 0.2 ml. of urine is measured into the bulb. Then enough 0.04 M H_2O_2 in 0.066 M phosphate buffer at pH 6.9 is added to the bulb to raise the liquid level 1 to 2 mm. above the bottom of the ground joint.

The manometer block, held in the left hand, is turned on edge with the ground joint down, and the capillary filled with water by opening the stopcock. When water runs from the end of the ground joint, one

finger of the left hand is placed over the top of the manometer to block the lumen, and the stopcock is closed. The bulb is then raised carefully up over the male portion of the ground joint until the bottom of the joint barely clears the surface of the liquid in the neck of the bulb. Then the joint is seated by a sudden jamming together of the two parts. No air bubbles should be introduced into the capillary during this procedure.

The bulb is fastened to the manometer with circles of rubber tubing, and a stop watch is started. The level of the liquid in the manometer is brought to zero by use of the levelling bulb, and shaking of the apparatus is started. After 15 minutes by the stop watch the shaking is stopped, and the manometer is read. The reading in milliliters multiplied by 1.13 gives the cubic millimeters of oxygen evolved in 15 minutes, provided that the machine is operated at a temperature near 25° C and that the capillary has a bore of 1 mm.

The bulb of the apparatus is cleaned after each use with 1 : 5 HNO_3 followed by thorough rinsing with distilled water. The manometer is also flushed out with distilled water. Every week or two the manometers and bulbs are cleaned with hot chromic acid cleaning solution and rinsed exhaustively. The glass beads used in the apparatus are cleaned in the same way as the bulbs (47).

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