DEC 18 1967

MASTER

PROGRESS REPORT

This report covers the results of experiments carried out by Dr. Kazuo Nomiyama in collaboration with Dr. E. C. Foulkes in the Department of Environmental Health at the University of Cincinnati. Dr. E. Pfitzer acted as project consultant.

The renal toxicology of uranium has been studied in considerable detail in earlier work. It was the aim of the present investigation to apply some of the more modern techniques and concepts of renal physiology to the study of uranium effects on the kidney, both in vivo and in vitro. The in vitro studies, utilizing kidney slices and isolated tubule preparations, incubated at 37° in suitable buffer solutions and in the presence or absence of uranium, did not lead to clear-cut results. A major experimental difficulty here arose, as expected, from the insolubility of uranium salts in physiological buffer solutions. Keeping the uranium in solution in acetate buffers of low pH provides only a partial answer because it raises the problem of the effects of unphysiologically low pH values on sensitive cells. As outlined in the proposal for future work we plan certain other experiments with isolated systems in vitro. The major portion of the present report, however, as well as the projections for future studies will focus on experiments with animals poisoned by intravenous administration of uranyl acetate.

Preliminary experiments had shown that under our conditions the intravenous injection of 0.2 mg $UO_2$/kg body weight consistently led within 2 days to an animal with grossly diminished renal function: The major functional abnormality observed was a fall in the maximal ability of the kidney to excrete paraminohippurate. The effect on glomerular function was less marked.

1. Effect on Glomerular Function.

Two days after injection the creatinine clearance of our animals had decreased to 50 to 60% of control levels. Interestingly the inulin clearance fell significantly less to approximately 70% of normal. In the control animals, both under free-flow and under stop-flow conditions, we consistently observed clearance ratios of creatinine to inulin $\left(\frac{U/P\ Cr}{U/P\ In}\right)$ approximately equal to 1.0. This ratio was decreased to 0.6-0.7 after uranium intoxication. A preliminary interpretation of this finding suggests that damage to the tubular epithelium permits back diffusion especially of smaller molecules (creatinine) from tubular fluid to blood. In order to test this possibility further we are now comparing the clearance ratios of a group of nonreabsorbed and nonsecreted sugars including mannitol, sucrose, raffinose. More details of these experiments are described in the renewal application.

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

## DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

**DISCLAIMER**

**Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.**

2. Effect on Tubular Function.

A decreased $T_{mPAH}$ presumably reflects damage to the secreting mechanism responsible for PAH secretion in the proximal tubule. We have also observed a decreased maximal glucose reabsorption and can thus confirm fully under our conditions earlier results in the literature. Removal of the kidneys from animals two days after uranium administration, and the kinetic study of PAH transport in slices and tubular fragments prepared from these kidneys has led to the following conclusions:

There is a highly significant depression of PAH transport at the level of the peritubular cell membrane. Thus we find that the rate constant of this reaction is greatly reduced. On the other hand the rate constant describing the intracellular PAH accumulation remained unchanged. Similarly, we could not observe a depression of the rate constant describing the transfer of PAH from cell across the luminal cell membrane into the tubular fluid. In agreement with the finding of a strong depression of influx, with an essentially unchanged ability to transfer PAH from cell into urine we find that the ability of the rabbit kidney to accumulate intracellular PAH in vivo is strongly depressed. It is clear that in the reverse case, i.e. inhibition of PAH flux from cell into lumen, without concomitant depression of PAH uptake across the peritubular cell membrane, we should find a continued high intracellular PAH accumulation.

The significance of these findings arises from the implied suggestion that one of the sites of attack of uranium on the cells of the proximal tubule lies on the peritubular side rather than on the luminal side as might have been expected from present views of the mechanism of action of uranium. The question whether such an effect on the peritubular side results from blood born uranium rather than uranium in the tubular fluid is the object of continuing experiments and is discussed further in the renewal proposal.

We are in the process of preparing at this time a more detailed manuscript describing the results obtained so far.

**LEGAL NOTICE**

This report was prepared as an account of Government sponsored work. Neither the United States, nor the Commission, nor any person acting on behalf of the Commission

A. Makes any warranty or representation, expressed or implied, with respect to the accuracy, completeness, or usefulness of the information contained in this report, or that the use of any information, apparatus, method, or process disclosed in this report may not infringe privately owned rights; or

B. Assumes any liabilities with respect to the use of, or for damages resulting from the use of any information, apparatus, method, or process disclosed in this report.

As used in the above, "person acting on behalf of the Commission" includes any employee or contractor of the Commission, or employee of such contractor, to the extent that such employee or contractor of the Commission, or employee of such contractor prepares, disseminates, or provides access to, any information pursuant to his employment or contract with the Commission, or his employment with such contractor.


RECEIVED
NOV 29 1957