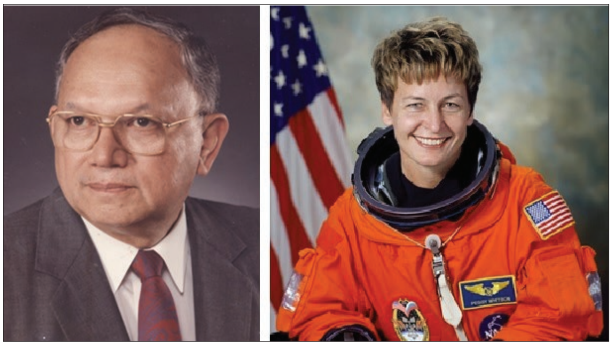

Dr. Abraham Cockett (left) [Courtesy of the University of Rochester Medical Center, Department of Urology] and Dr Peggy Whitson (right) [Courtesy of NASA]

A history of urolithiasis risk in space

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Introduction: *The development of renal stones in space would not only impact the health of an astronaut but could critically affect the success of the mission.*

Materials and methods: *We reviewed the medical literature, texts and multimedia sources regarding the careers of Dr. Abraham Cockett and Dr. Peggy Whitson and their contributions to the study of urolithiasis in space, as well as the studies in between both of their careers that helped to further characterize the risks of stone formation in space.*

Results: *Dr. Abraham T. K. Cockett (1928-2011) was Professor and Chair of the Department of Urology at the University of Rochester and served as AUA President (1994-1995). In 1962, Dr. Cockett was one of the first to raise a concern regarding astronauts potentially forming renal stones in space and suggested multiple prophylactic measures to prevent stone formation.*

Many of the early studies in this field used immobilized patients as a surrogate to a micro-gravity environment to mimic the bone demineralization that could occur in space in order to measure changes in urinary parameters. Dr. Peggy A. Whitson (1960-), is a biochemistry researcher and former NASA astronaut. She carried out multiple studies examining renal stone risk during short term space shuttle flights and later during long-duration Shuttle-Mir missions.

Conclusion: *From the early vision of Dr. Cockett to the astronaut studies of Dr. Whitson, we have a better understanding of the risks of urolithiasis in space, resulting in preventive measures for urolithiasis in future long duration space exploration.*

Key Words: history of urology, urolithiasis risk in space, bone demineralization, zero-gravity

Introduction

In 1957 the Soviet Union launched Sputnik, sparking the space race with the Cold War in the backdrop. They followed with sending Yuri Gagarin, the first human in space in 1961.[1] The United States responded with Project Mercury in which seven NASA test pilots would become the first U.S. astronauts. Tom Wolfe would immortalize their stories in his book *The Right Stuff*.[2] On May 25, 1961, President John F. Kennedy would give his famous speech challenging the country "to land a man on the moon and return him safely to earth" before the end of the decade. Alan Shepard became the first American in space in 1961 on Freedom 7. In 1962, John Glenn became the first American to orbit the Earth in Friendship 7. The Mercury Program ran

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from 1959-1963 and achieved its primary goal of orbital space flight. Project Gemini achieved longer durations of space flight, rendezvous and docking maneuvers and extravehicular activity, leading Edward White in 1965 to perform the first spacewalk. The next step was taken with the Apollo program on the back of the powerful Saturn V rocket. It culminated with Apollo 11 and the lunar module landing on the moon on July 20, 1969. Last year we celebrated the 50th Anniversary of the lunar landing. The Space Shuttle program ran from 1981 to 2011 totaling 135 flights. As we began to spend a longer time in space with Skylab, Mir and the International Space Station (ISS), our understanding of human physiology in space and space medicine began to grow.

Abraham T. K. Cockett, MD (1928-2011)

The first urologist to publish on the urologic implications in zero-gravity was Dr. Abraham T. K. Cockett. Dr. Cockett served as Chairman of the Department of Urology at the University of Rochester and was President of the AUA in 1994. He was a Captain in the United States Airforce and Chief of Experimental Medicine at the School of Aerospace Medicine in Texas. In a *Journal of Urology* paper in 1962 (during the time of the Project Mercury) he predicted that the existence of a weightless state would lead to severe derangements in calcium and phosphorus metabolism.[3] He stated that "relative immobilization, coupled with zero gravity, may produce significant derangements in phosphorus metabolism, in addition to decalcification of the bony skeleton, favoring formation of urinary calculi." He also was concerned about Vitamin A deficiency, which might lead to desquamation of the urothelium leading to a nidus for stone formation and excess Vitamin D absorption from ultraviolet light causing increased calcium absorption in the gastrointestinal tract.[4]

Not only did Dr. Cockett predict potential urologic problems in space but he proposed a number of prophylactic measures to help combat these problems including: a vigorous in-flight physical exercise program, rotation of the spacecraft to create artificial gravity, drugs to lower urinary pH, an adequate fluid intake and a rigid voiding schedule to avoid urinary stasis.[3] Of his proposed measures to combat stone formation, an in-flight physical exercise program, medications to increase urinary pH (potassium citrate) and adequate fluid intake have all been studied and found to reduce risk factors in stone formation.[5-7] Dr. Cockett was also a researcher in the NASA Biosatellite Program, having fitted Bonny, a primate, with a closed system urethral catheter during 8.5 days of space flight. The study noted urinary diuresis during spaceflight as well as an increase in inflight urinary calcium.[8]

Combating the effects of a simulated micro-gravity environment on stone risk

At the time of Dr. Cockett's research, the closest analog we had to a micro/zero-gravity environment were immobilized patients. In 1922, Paul et al reported on 20 cases of nephrolithiasis in men who developed renal calculi following war wounds where the patients were immobilized for prolonged periods of time. In that study, the time from a wound to the first symptom of stones was 17.7 months (531 days).[9] Kimbrough and Denslow in 1949 found 272 days as the mean time for interval stone development in immobilized patients. The mechanism of action for stone formation in this population was the mobilization of calcium from skeletal reserves.[10]

Dr. Charles Y. K. Pak, a Professor of Internal Medicine at the University of Texas Southwestern, is a world-renowned leader in mineral metabolism research and the medical management of kidney stones and osteoporosis. Dr. Pak performed a double-blinded placebo-controlled trial that showed the benefits of potassium-magnesium citrate in decreasing calcium oxalate supersaturation in patients placed on 5 weeks of bedrest.[11] Dr. Pak and colleagues further carried out a randomized placebo-controlled trial of 16 male subjects who received 20 mg of alendronate or placebo during three weeks of strict bedrest. The alendronate treated patients showed lower urinary calcium excretion compared to the placebo group.[12] Dr. Manoj Monga and colleagues performed a study to evaluate the risk of stone formation in a simulated microgravity environment.[13] His study population was 11 sets of identical twins who were placed on bedrest for 30 days. One twin per pair was allowed to exercise while supine in a lower body negative pressure chamber (40 minutes per day for 6 days a week). The authors found that urinary calcium increases after just 1 week in the non-exercise control group and no increase in the exercise group. Calcium oxalate supersaturation significantly increased in the non-exercise groups. Dr. Monga's study showed that exercise in a simulated microgravity environment prevented an increase in urinary calcium excretion.[13] Dr. Pak and Dr. Monga's studies showed that potassium-magnesium citrate, bisphosphonate therapy and exercise could be used to decrease urinary stone risk factors (calcium oxalate supersaturation and urinary calcium excretion) in a simulated micro-gravity environment.[11-13]

Time in space

One of the most significant risk factors for stone formation in astronauts is their length of time in space. The longest time continuously spent in space was 437 days by Valeri Polyakov. The longest cumulative time spent in space was Gennady Padalka at 878 days (5 missions).[14] A study of three crewmen (the commander, scientist pilot and pilot) from Skylab 2, 3 and 4 showed that mineral losses do occur from the bones of the lower extremities during space missions of up to 84 days and that in general, they follow the bone loss patterns of the bed-rested situation.[15]

We have come a long way from the short mission lengths of the Apollo and Space Shuttle. If we are to travel to Mars, just the round trip will take approximately 400-450 days, and we only have one human that approached that in continuous time spent in space.

We know that 12 NASA astronauts have developed 14 post-flight stones and only one cosmonaut, Anatoly Berezovoy aboard the Salyut-7 space station, has been thought to have formed a stone in space. It is believed he passed his stone without intervention though the stone was never recovered, thus nearly avoiding to have to abort the mission.[16,17]

When looking at other etiologies for stone formation, we have to look at astronaut nutrition and hydration. Astronauts have shown decreased fluid intake during shuttle missions as they can experience relative dehydration or space motion sickness during the early phases of space flight until the body adjusts. Though nutritional recommendations for crew members during space flight include a fluid intake of > 2 L/day, there has previously been poor compliance likely due to heavy workloads and extra-vehicular activity.[18] Living on a space station also brings with it some limitations. There is no refrigeration and thus no long term available fresh fruits and vegetables, a good source of dietary citrate. Foods are packaged in single-serving containers, and earlier foods had significant sodium content, which NASA has worked hard to decrease in U.S. food items to approximately 3 g/day.[19] Vitamin D is a critical nutrient for astronauts on long-duration space flights as they lack both a good food source of Vitamin D and ultraviolet light exposure, as spacecrafts are shielded to block ultraviolet light. Thus vitamin D supplements (800 IU per day) are provided for crew members.[19] A study evaluating nutrition and exercise in space found that crew members that ate well (> 90% of estimated energy requirements), had adequate Vitamin D status and exercised using the "Advanced Resistive Exercise Device" maintained bone mineral density after 4 to 6 month space missions.[7]

Peggy A. Whitson, PhD

Dr. Peggy A. Whitson is a biochemistry researcher, NASA astronaut and former NASA chief astronaut. Dr. Whitson completed three extended missions aboard the International Space Station, serving as the station commander for Expeditions 16 and 51. She spent a total of 665 days in space, the longest time in space for an American astronaut, and performed ten spacewalks.[20] She has carried out numerous studies exploring the risk of stone formation in astronauts, including multiple collaborations with Dr. Charles Pak.[6,21]

She examined 24-hour urine collections in astronauts at different time points during a shuttle mission and characterized an initial decrease in urine volume early in space flight as the body adjusts to the zero-gravity environment as well as an increase in calcium oxalate supersaturation during early and late space flight.[6] This effect normalized 7-10 days after landing. She also examined the pre and post flight 24-hour urines of 332 Shuttle crew members—finding an increase in urinary calcium and oxalate, a decrease in urinary citrate and decreased urine volume.[21]

In a retrospective analysis of 24-hour urine samples collected before launch and immediately after landing from the Longitudinal Study of Astronaut Health (LSAH) database, Dr. Whitson and colleagues analyzed the urinary characteristics associated with those astronauts that formed renal stones.[16] Fourteen renal stone episodes occurred in 12 U.S. astronauts (ten men, two women) with nine stone events occurring in seven crew members post-flight (two crew members had two post-flight stones). The length of time for the appearance of symptomatic stone formation ranged from 9 to 120 months. Six of the post-flight stones occurred since 1994 with the beginning of the extended shuttle missions of greater than twelve days in space. Results of the urinary chemistries prior to stone formation in the 12 stone-forming astronauts showed that five of the astronauts had hypercalciuria, five had low urine volume (< 2 L/day), and six astronauts had an elevated urinary supersaturation. When examining post-flight urinary chemistries of 10 stone-forming astronauts who flew on space shuttle missions ranging from 3-16 days, the post-flight analysis showed that all crew members experienced increased urinary calcium levels compared to preflight levels. Six astronauts showed hypercalciuria, four had hyperoxaluria and four had post-flight urine volumes less than 2 L/day. Eleven of the 12 astronauts had one or more increased risk factors associated with stone formation. Chemical analysis of stones recovered after treatment or spontaneous passage demonstrated that the majority of post-flight stones were "mixed stones composed mainly of calcium oxalate," with one pure uric acid stone.[16]

When analyzing pre and post-flight 24-hour urinary collections in U.S. space shuttle crew members in the LSAH database, the incidence of hypercalciuria increased from pre-flight to post-flight collections from 21% to 39%. Increases in pre-flight to post-flight hypocitraturia (7% to 14%), low urine volumes (< 2 L/day; 52% to 59%) and elevated calcium oxalate supersaturation (26% to 80%) were observed.[16]

Furthermore, Dr. Whitson carried out a double-blind placebo-controlled trial studying the effect of potassium citrate (20 mEq daily) vs placebo on 30 long-duration crew members in the Mir and International Space Station.[5] Potassium citrate treated crew members had decreased urinary calcium excretion and maintained preflight calcium oxalate supersaturation risk compared to controls. The study showed that potassium citrate may decrease the risk of renal stone formation during and immediately after spaceflight, Table 1.

Diagnosis and treatment of stones in space

A diagnostic modality is available on the International Space Station: "A flight class I, rack-mounted Philips/ Advanced Technologies Laboratory model HDI-5,000 ultrasound imaging unit" can be used by the crew member medical officer on board with ground guidance consisting of a radiologist and urologist.[22]

TABLE 1. **Dr. Whitson's Space Shuttle and International Space Station Studies**

Study	**No. astronauts**	**Time in space**	**Measurement**	**Results**
J Urol 1993	86 (76 male, 10 female)	Missions < 6 days vs. 6-10 day missions	24-hr urine 10 days before launch vs. on landing day	•Urinary pH decreased (5.98 to 5.58, p<0.0001) •Urinary calcium increased (190 to 213, p < 0.05) •Urinary citrate decreased (707 to 575, p < 0.0005)
J Urol 1997	6 space Shuttle crew members	11-16 day space Shuttle mission	24-hr urine before flight, early in-flight (days 2-4), late in-flight (days 10-13), landing day and 7-10 days after landing	•Total urine volume decreased during early in-flight phase (1.7 L/day preflight to 0.8 L/day early in-flight, NS) •Urinary calcium levels increased during space flight and upon landing (pre-flight =166.2 mg/day to landing day = 245.2 mg/day, p < 0.05) •CaOx SS increased during early in-flight and remained elevated throughout space flight (pre-flight = 1.52, early in-flight = 2.95, late in-flight = 2.78, p < 0.05)
J Urol 2009	30 crew members on MIR and ISS (18 controls, 12 received KCit)	NASA-Mir missions (12 crew): 129 to 208 days ISS missions (18 crew): 93 to 215 days	24-hr urine performed before launch, early flight (< 35 flight days), mid flight (36 to 120 days), late flight (> 120 days) and on landing day and two additional days within 18 post-flight days	Crew members ingesting KCit, compared to placebo had: •Decreased calcium excretion (p < 0.05) •Increased urinary pH (p < 0.05) •Lower CaOx and uric acid SS (p < 0.05)

NS = did not reach significance (p > 0.05); KCit = potassium citrate; CaOx = calcium oxalate; ISS = International Space Station; SS = super saturation

A presentation by NASA scientists in 2008 concluded that the risks of developing stones in space were significant and that "A properly developed approach to selection, monitoring, and preventative medicine with effective countermeasures, along with a readily implantable protocol of early imaging diagnosis and minimally-invasive contingency intervention, should prevent GU issues, such as urinary calculi from having a significant mission impact for exploration-class space flight."[22] Thus, at the time, NASA's primary approach to stone formation in space was preventative.

That approach changed when Dr. Michael Bailey, PhD, and his group at the University of Washington developed an ultrasound-based stone management system to detect stones with S-mode ultrasound imaging, break stones with burst wave lithotripsy and reposition stone with ultrasonic propulsion.[23] His research is being sponsored by NASA and the National Space Biomedical Research Institute with hopes for application in space.

From the early vision of Dr. Cockett to the astronaut studies of Dr. Whitson we have begun to better understand the role that bone demineralization, dehydration and stasis play in the risk for urolithiasis in space so that we can work to prevent urolithiasis in future long-duration space exploration. □

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