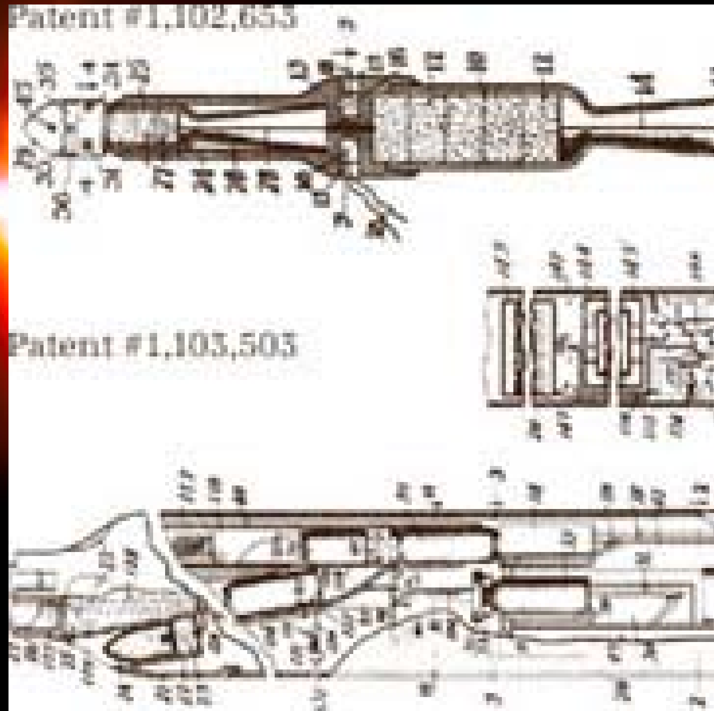
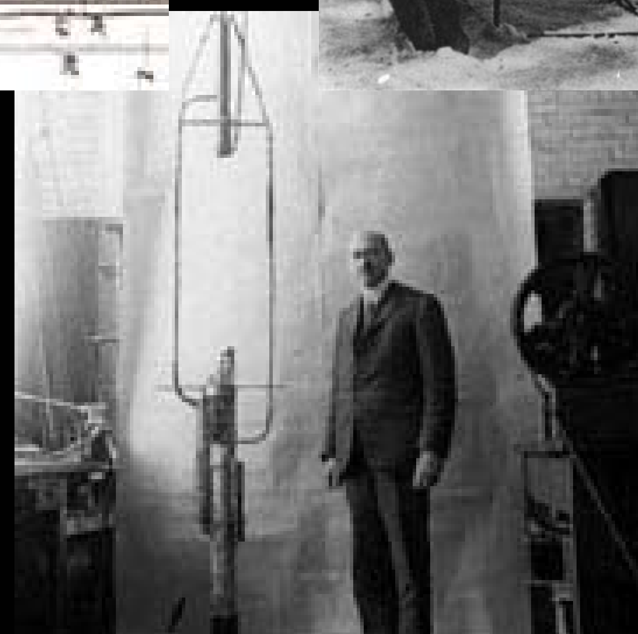
# Pharmacology in Spaceflight

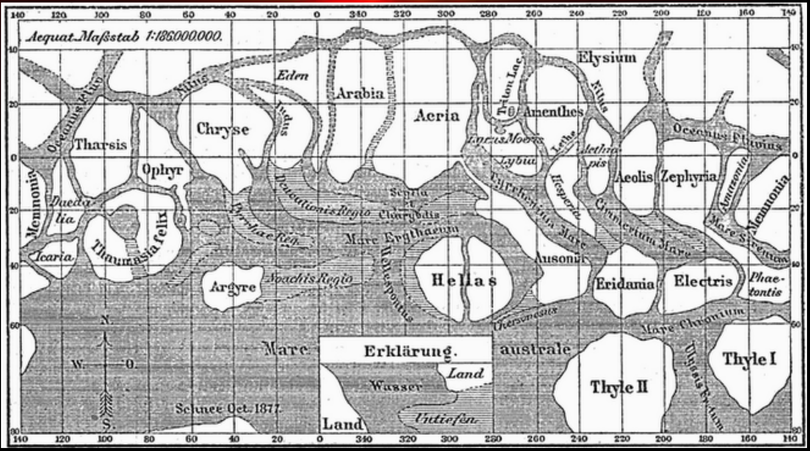
July 14, 2011

V. Wotring, PhD
Pharmacology Discipline Lead
NASA JSC



July 14, 1914 1st patent for liquid-fueled rocket design granted to Dr. Robert Goddard




Before 7/14/1965

7/14/1965

<u>July 14, 1965</u>: After a journey of eight months, NASA's space probe, Mariner 4, flew within 6,118 miles of Mars and provided the first close-up images of the Martian surface

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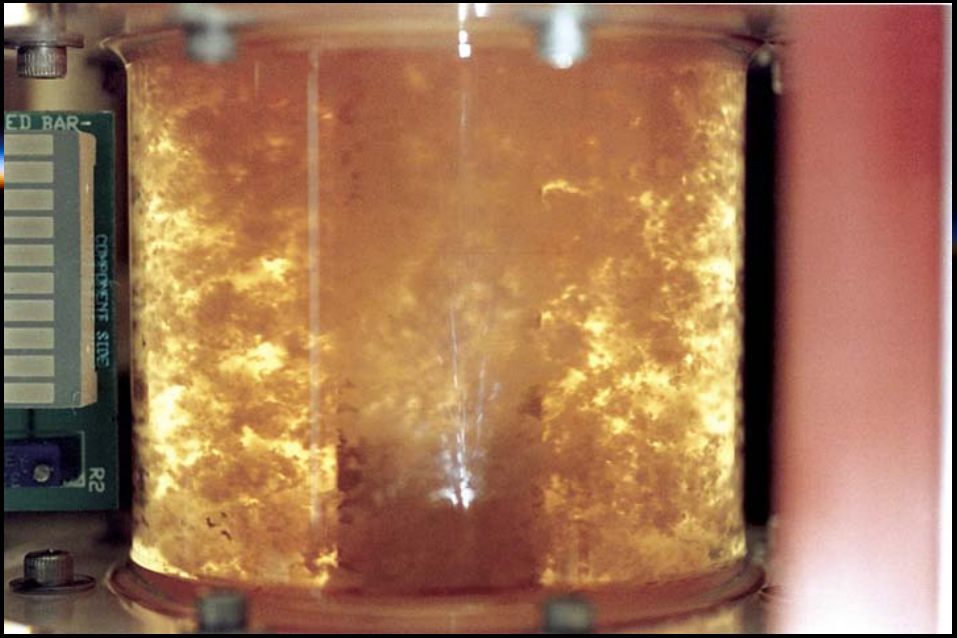
July 14,1995: FD2 STS-70

●Physiological and Anatomical Rodent Experiment / National Institutes of Health-Rodents (PARE/NIH-R) behavioral changes and the development of muscle, bone, nervous, and circadian timing systems in rats exposed to microgravity *in utero*. This project emphasized features of the rat's behavior and physiology that are known to contribute to successful pregnancy, labor, delivery and the onset of postnatal care, especially lactation. In addition, examination of the offspring after birth is expected to provide information about the earliest development of the vestibular system under gravity as compared to microgravity conditions.

●Commercial Protein Crystal Growth (CPCG)

●Biological Research in Canisters (BRIC BRIC-04 experiments were specifically designed to examine how the hormone system and muscle formation processes of the tobacco hornworm are affected an altered gravitational field. BRIC experiment specimens were exposed to the temperatures, carbon dioxide, oxygen, atmospheric pressure and humidity conditions of the middeck.




- Bioreactor Demonstration System (BDS)
- Space Tissue Loss/National Institutes of Health-Cells (STL/NIH-C) the effects of microgravity on embryogenesis in the Medaka fish egg at the molecular level. Of particular interest was the digital image capture of the gastrulation development phase; images were captured via the STL-B on board video microscope and telemetered to investigators on the ground. This follow-up experiment helped validate previous findings, as well as provided additional definition to the model for future space biology experimentation.

**Spaceflight in humans alters autonomic regulation of arterial pressure**

JANICE M. FRITSCH-YELLE, JOHN B. CHARLES, MICHELE M. JONES, LARRY A. BEIGHTOL, AND DWAIN L. ECKBERG

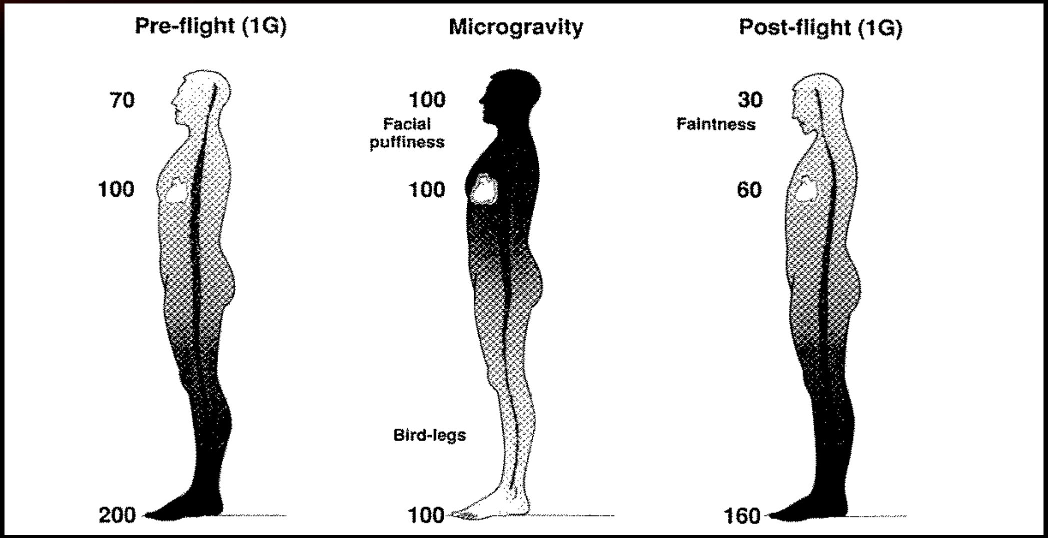
J. Appl. Physiol. 77(4): 1776-1783,1994

Spaceflight is associated with decreased orthostatic tolerance after landing. Short-duration spaceflight (4-5 days) impairs one neural mechanism: the carotid baroreceptor-cardiac reflex. To understand the effects of longer-duration spaceflight on baroreflex function, we measured R-R interval power spectra, antecubital vein plasma catecholamine levels, carotid baroreceptor-cardiac reflex responses, responses to Valsalva maneuvers, and orthostatic tolerance in 16 astronauts before and after shuttle missions lasting 8-14 days. We found the following changes between preflight and landing day: 1) orthostatic tolerance decreased 2; ) R-R interval spectral power in the 0.05 to 0.15 Hz band increased; 3) plasma norepinephrine and epinephrine levels increased; 4) the slope, range, and operational point of the carotid baroreceptor cardiac reflex response decreased and 5) blood pressure and heart rate responses to Valsalva maneuvers were altered. Autonomic changes persisted for several days after landing. These results provide further evidence of functionally relevant reductions in parasympathetic and increases in sympathetic influences on arterial pressure control after spaceflight.

Other life sciences experiments performed during the STS-70 mission were space motion sickness, cardiovascular deconditioning, muscle loss, changes in coordination and balance strategies, radiation exposure, pharmacokinetics and changes in the body's biochemistry.

# Physiology in Space

Decreased gravity makes body fluids shift upward




Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight☆

Alan R. Hargens[a,*], Sara Richardson[b]

*Respiratory Physiology & Neurobiology 169S (2009) S30–S33*

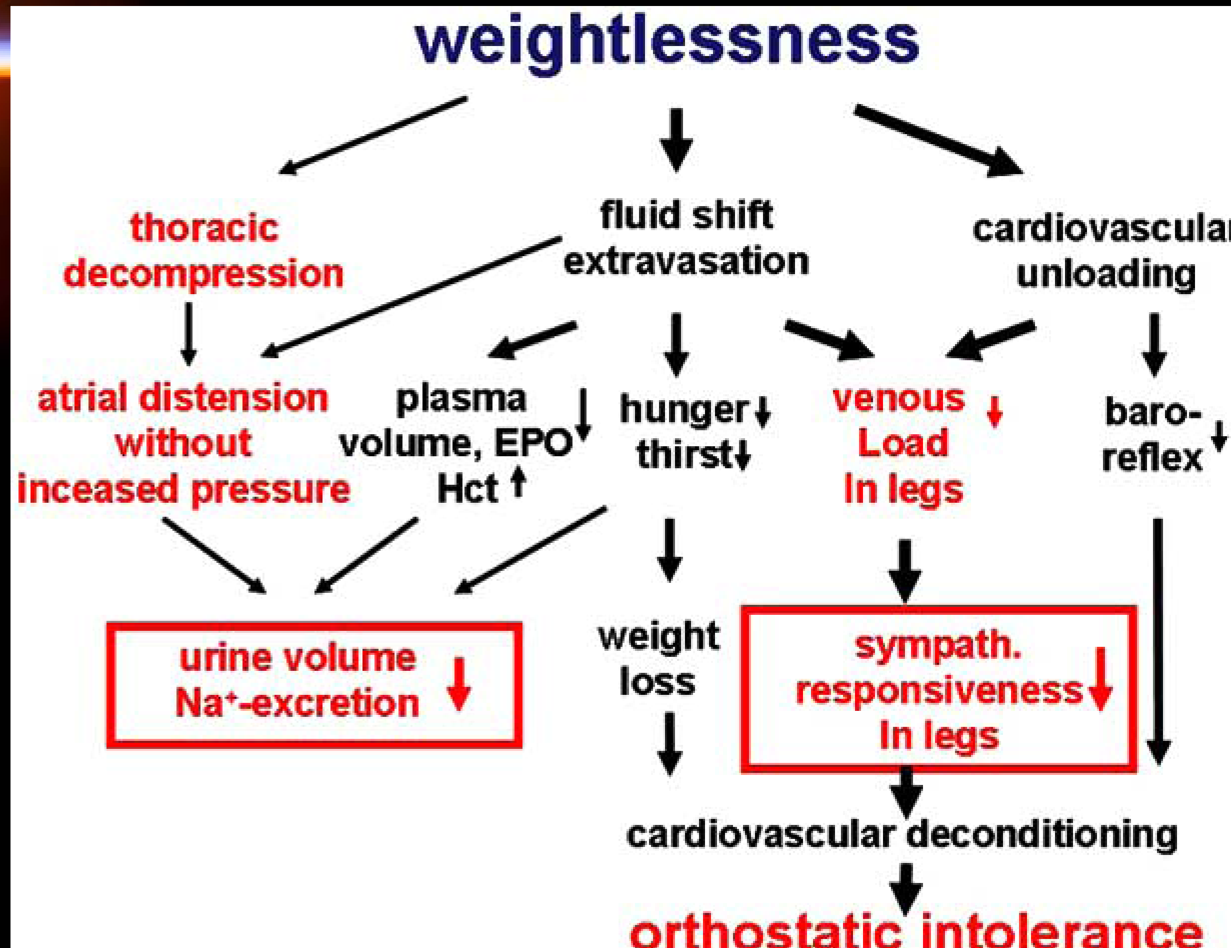
# Physiology in Space

Head Congestion


"In space, you're always on the verge of a headache."

David Wolf

# Physiology in Space



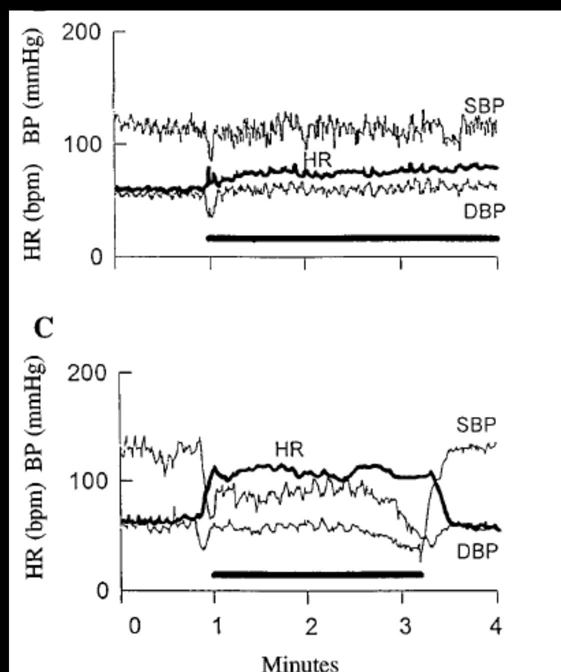

Regulation of Body Fluid and Salt Homeostasis –

from Observations in Space to New Concepts on Earth

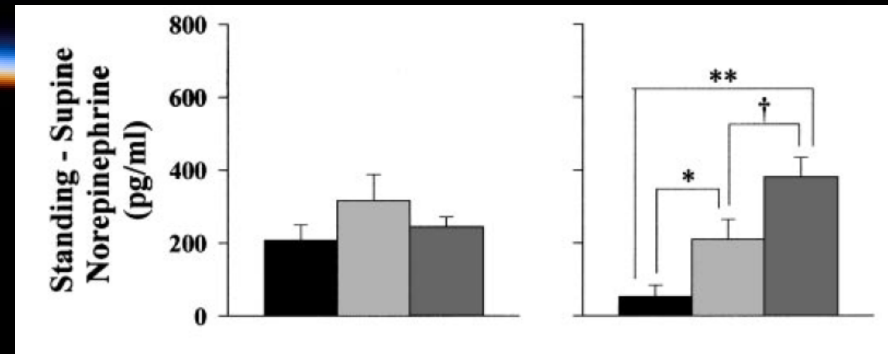
R. Gerzer* and M. Heer *Current Pharmaceutical Biotechnology, 2005, 6, 299-304 299*

# Cardiovascular Changes in Spaceflight

Tracings during a tilt test from an astronaut preflight (top) and on landing day (lower). Horizontal bars are the time in upright posture




Fritsch-Yelle, Janice M., Peggy A. Whitson, Roberta L. Bondar, and Troy E. Brown. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. *J. Appl. Physiol. 81(5): 2134–2141, 1996.*

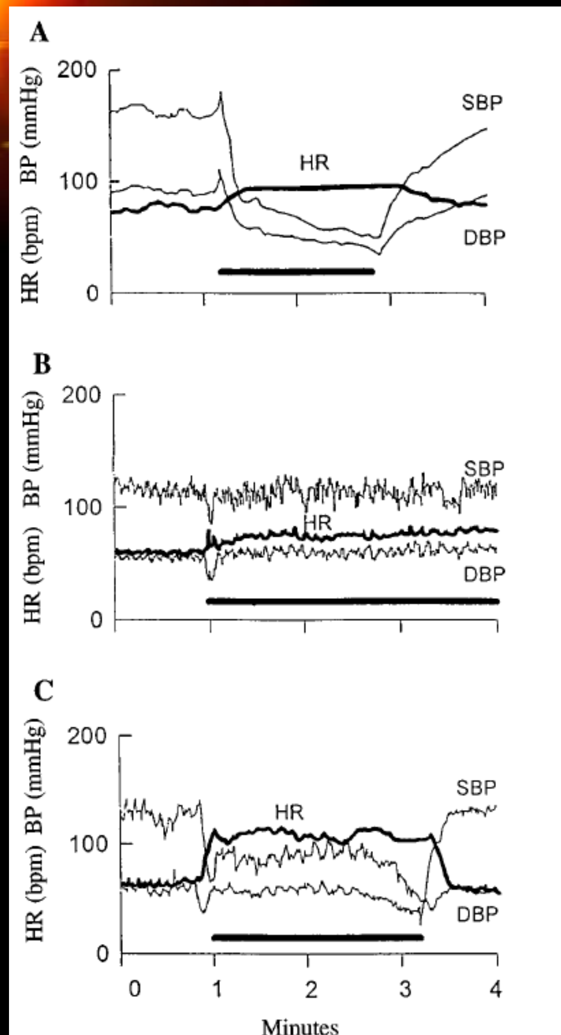



Plasma norepinephrine (*top)* and epinephrine (*bottom) responses in* women (*n  4; black bars), presyncopal* men (*n  6; light gray bars), and nonpresyncopal* men (*n  22; dark gray* bars) when tested preflight (*A), on* landing day (B), and 3 days postspaceflight (*C). Values are means SE. †P  0.058. *P  0.05. **P  0.01*

Waters, Wendy W., Michael G. Ziegler, and Janice V. Meck. Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J Appl Physiol 92: 586–594, 2002.*

# Cardiovascular Changes in Spaceflight

Tracings during a tilt test from a patient with autonomic failure (A), and an astronaut preflight (B) and on landing day (C). Horizontal bars are the time in upright posture

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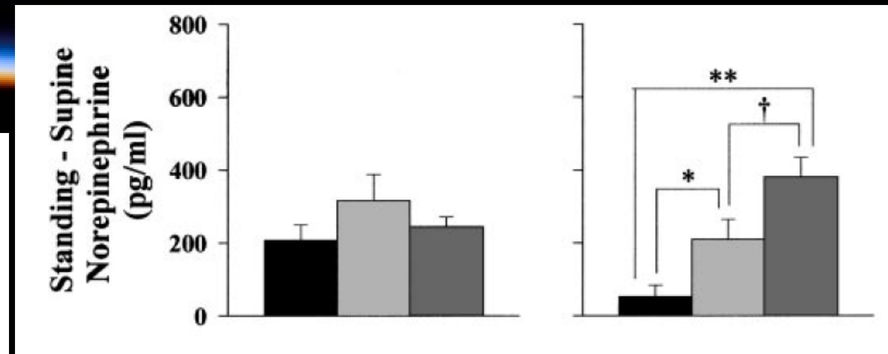


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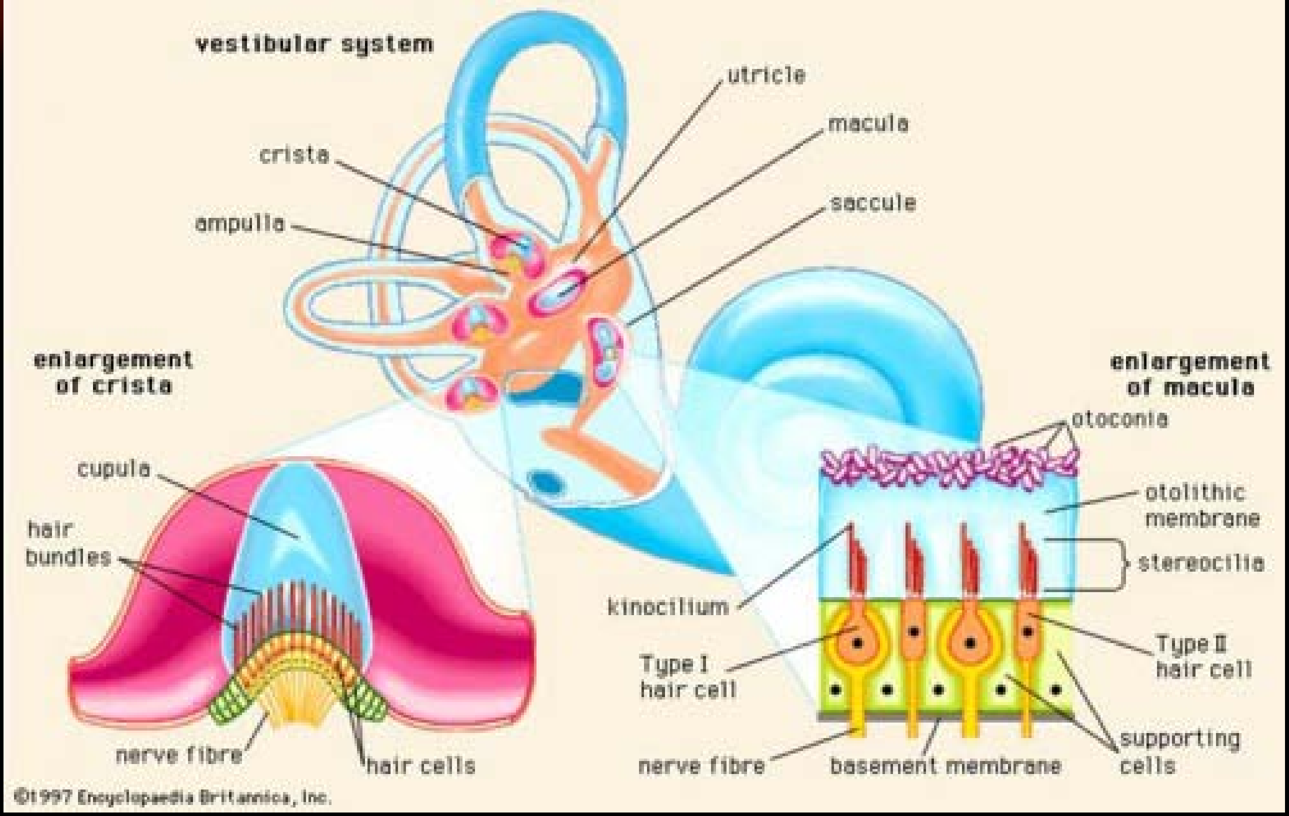
# Physiology in Space

## Decreased gravity disrupts the sense of balance




http://www.skybrary.aero/index.php/Vestibular_System_and_Illusions_(OGHFA_BN)

# Physiology in Space

## Space Motion Sickness (Space Adaptation Syndrome)

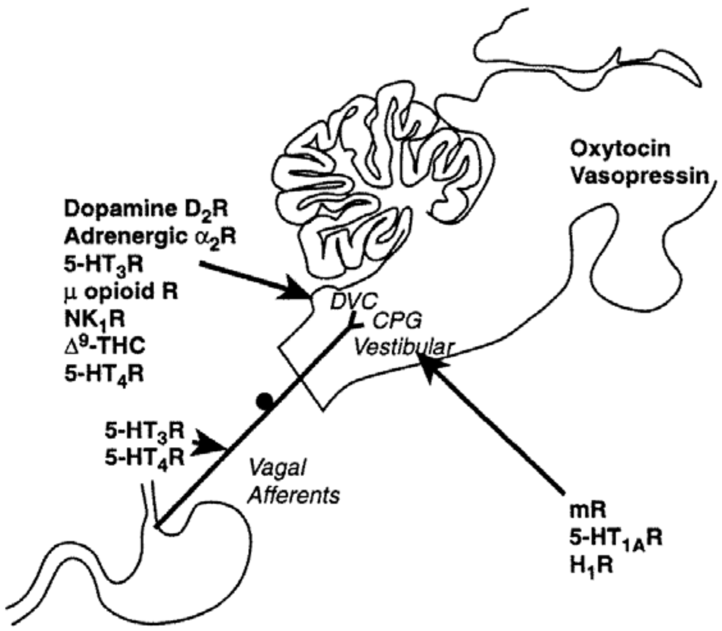


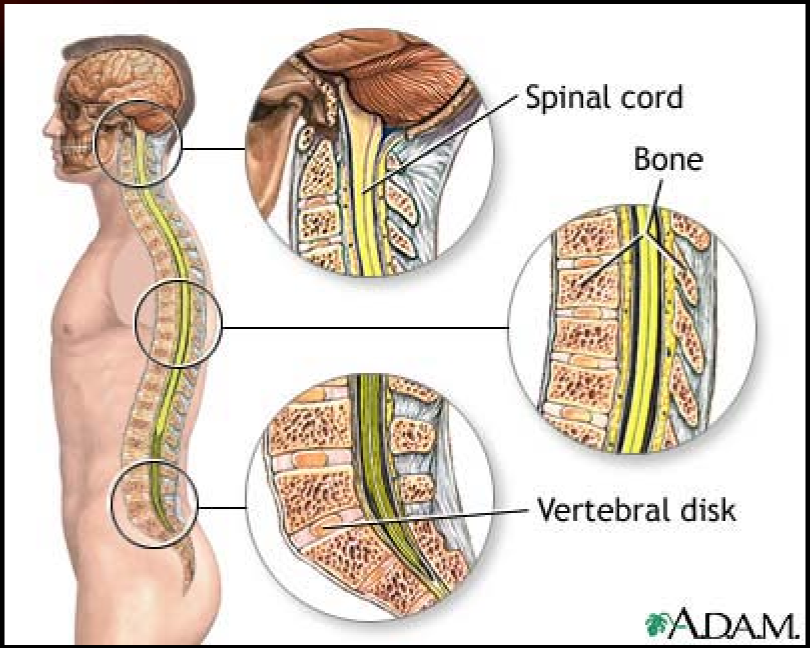

**Figure 3.** Selected drugs that affect emesis and their site(s) of action (if known). $\alpha_2R$ = adrenergic $\alpha_2$-receptor; CPG = central pattern generator; $D_2R$ = dopamine$_2$-receptor; $\Delta^9$-THC = $\Delta^9$-tetrahydrocannabinol; DVC = dorsal vagal complex; 5-HT = serotonin; H = histamine; mR = cholinergic muscarinic receptor; NK = neurokinin; R = receptor.

Am J Med. 2001 Dec 3;111 Suppl 8A:106S-112S.

Central neurocircuitry associated with emesis. Hornby PJ.

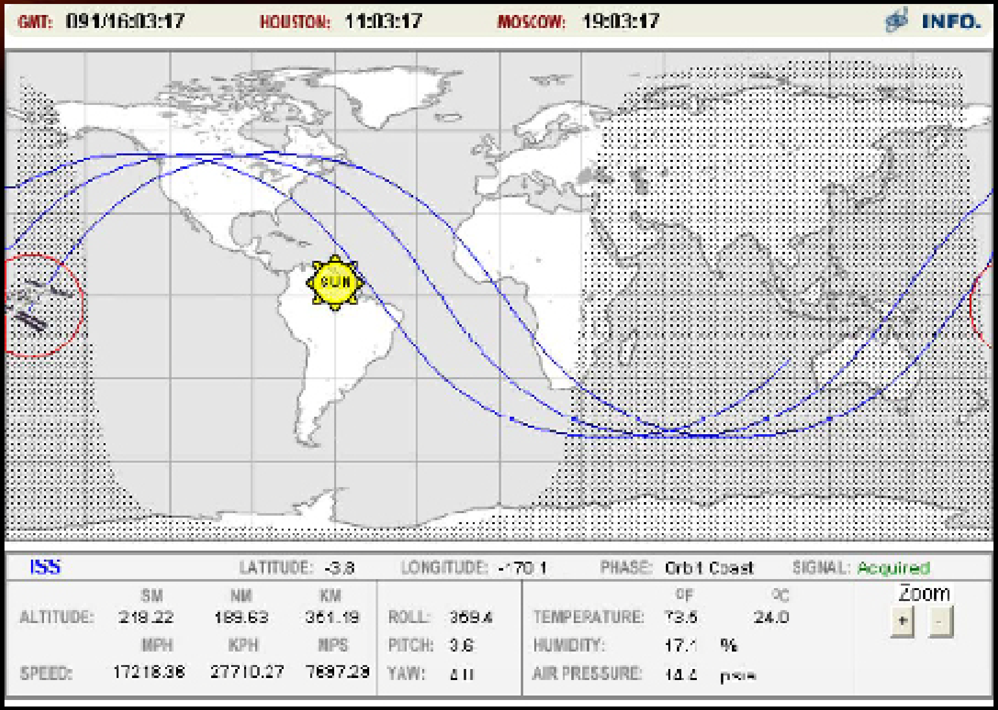
# Physiology in Space

## Body Pain



# Physiology in Space

## Circadian Rhythm Disruption



# Physiology in Space

Russian ground personal members and doctors carry Italian ESA astronaut Roberto Vittori to the medical tent upon his arrival to the town of Arkalyk, northern Kazakhstan, early Monday, April 25, 2005. [AP]

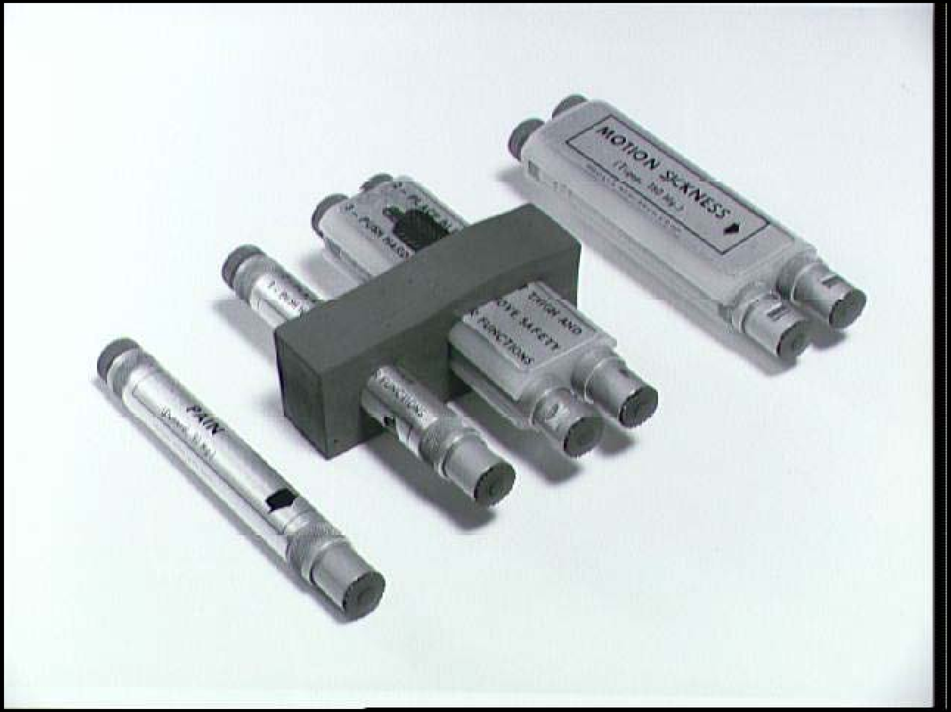
# First pharmaceuticals in US spaceflight

1963 Mercury Atlas 9

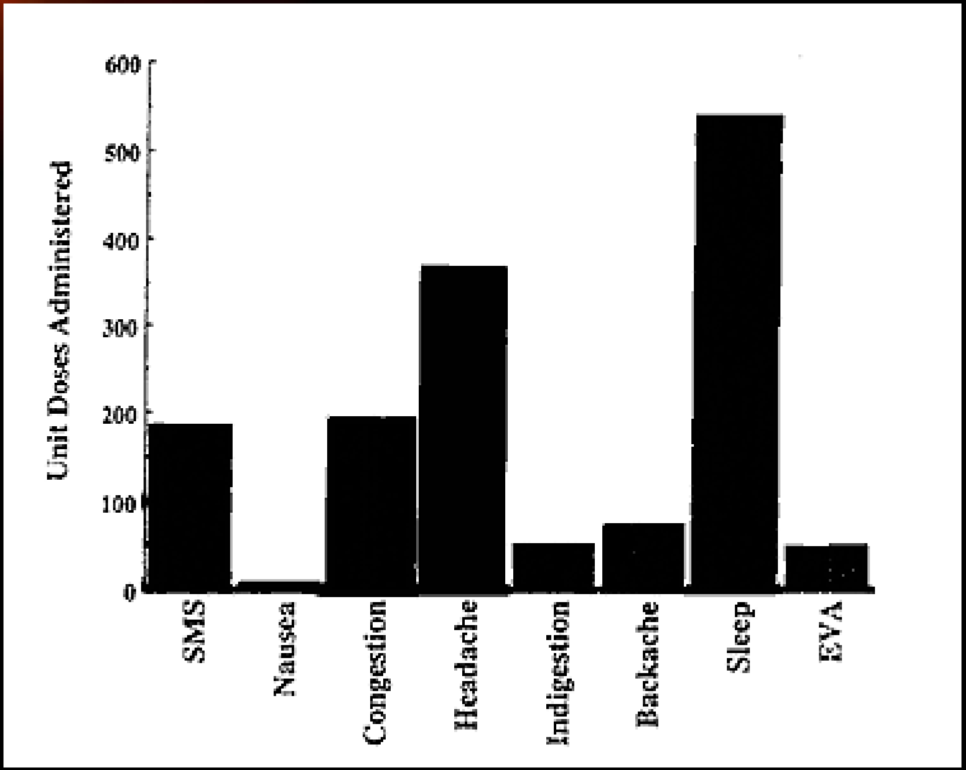
Gordon Cooper carried pre-loaded drug injectors in space suit pocket

Demerol – pain relief

Tigan  - motion sickness



# Pharmaceutical Use on Shuttle




PUTCHA L, BERENS KL, MARSHBURN TH, ORTEGA HJ, BILLICA RD. *Pharmaceutical use by U.S. astronauts on space shuttle missions.* Aviat Space Environ Med 1999; 70:705–8.


OXYMETAZOLINE
(AFRIN)
0.5%, 15 ml
P/N:
Qty: 12 each
Lot:
Exp. Date:
ALIAS: Ambien
Zolpidem
10mg
P/N: XXXXXXXXXXXX
Qty: 250 tablets
Exp. Date: XX/XX/XXXX
ALIAS: Claritin
Loratadine
10 mg
P/N: XXXXXXXXXXXX
Qty: 75 tablets
Exp. Date: XX/XX/XXXX
ALIAS: Refresh eye drops
Hydroxymethyl-cellulose (Refresh plus)
0.0040%
P/N: XXXXXXXXXXXX
Qty: 40 unit doses
ASPIRIN
(BAYER)
325 mg
P/N:
Qty: 120 each
Lot:
Exp. Date:

ESMOEPRAZOLE
(NEXIUM)
40 mg
P/N:
Qty: 30 each
Lot:
Exp. Date:
SERTRALINE
(ZOLOFT)
50 mg
ALIAS: Valacyclovir
(Valtrex)
1 mg
P/N: XXXXXXXXXXXX
Qty: 60 tablets
Exp. Date: XX/XX/XXXX
TAMULOSIN
0.4 mg
P/N:
Qty: 10 each
Lot:
Exp. Date:
ALIAS: Estrogen
(Premarin)
1.25 mg
LORAZEPAM
(ATIVAN)
1 mg
P/N:
Qty: 50 each
Lot:
Exp. Date:

ALIAS: Provigil
Modafinil
200 mg
P/N: XXXXXXXXXXXX
Qty: 40 tablets
Exp. Date: XX/XX/XXXX
ALIAS: Melatonin
(Melatonin)
3 mg
P/N: XXXXXXXXXXXX
Qty: 200 tablets
Exp. Date: XX/XX/XXXX
PSEUDOEPHEDRINE
(SUDAFED 12 hour)
120 mg
P/N:
Qty: 125 each
Lot:
Exp. Date:
ALIAS: Imodium
(Loperamide)
2 mg
P/N: XXXXXXXXXXXX
Qty: 40 tablets
Exp. Date: XX/XX/XXXX
IBUPROFEN
(MOTRIN)
400 mg
P/N:
Qty: 500 each
Lot:
Exp. Date:
PROMETHAZINE
(PHENERGAN,
25 mg/ml, 1 ml
P/N:
Qty: 12 each
Lot:
Exp. Date:
ALIAS: Tylenol
Acetaminophen
325 mg
Qty: 25 bags of 10
Exp. Date: XX/XX/XXXX

# Our Mission at the JSC Pharmacology Lab…

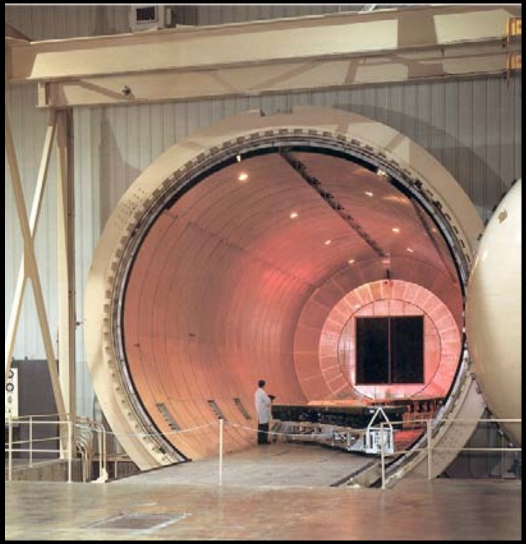
…to ensure that flight surgeons have good information about how administered pharmaceuticals will work in the extreme conditions of spaceflight

…which means that we have to understand the physiological changes caused by living in the spaceflight environment

…as well as the effect of the spaceflight environment on the stored drugs themselves

…as well as the pharmaceuticals' mechanism of action

1. Design experiment to answer the scientific question.
2. Book the appropriate time in NASA's top-secret low-gravity chamber on Earth.
3. Analyze results and make recommendations to flight medicine.



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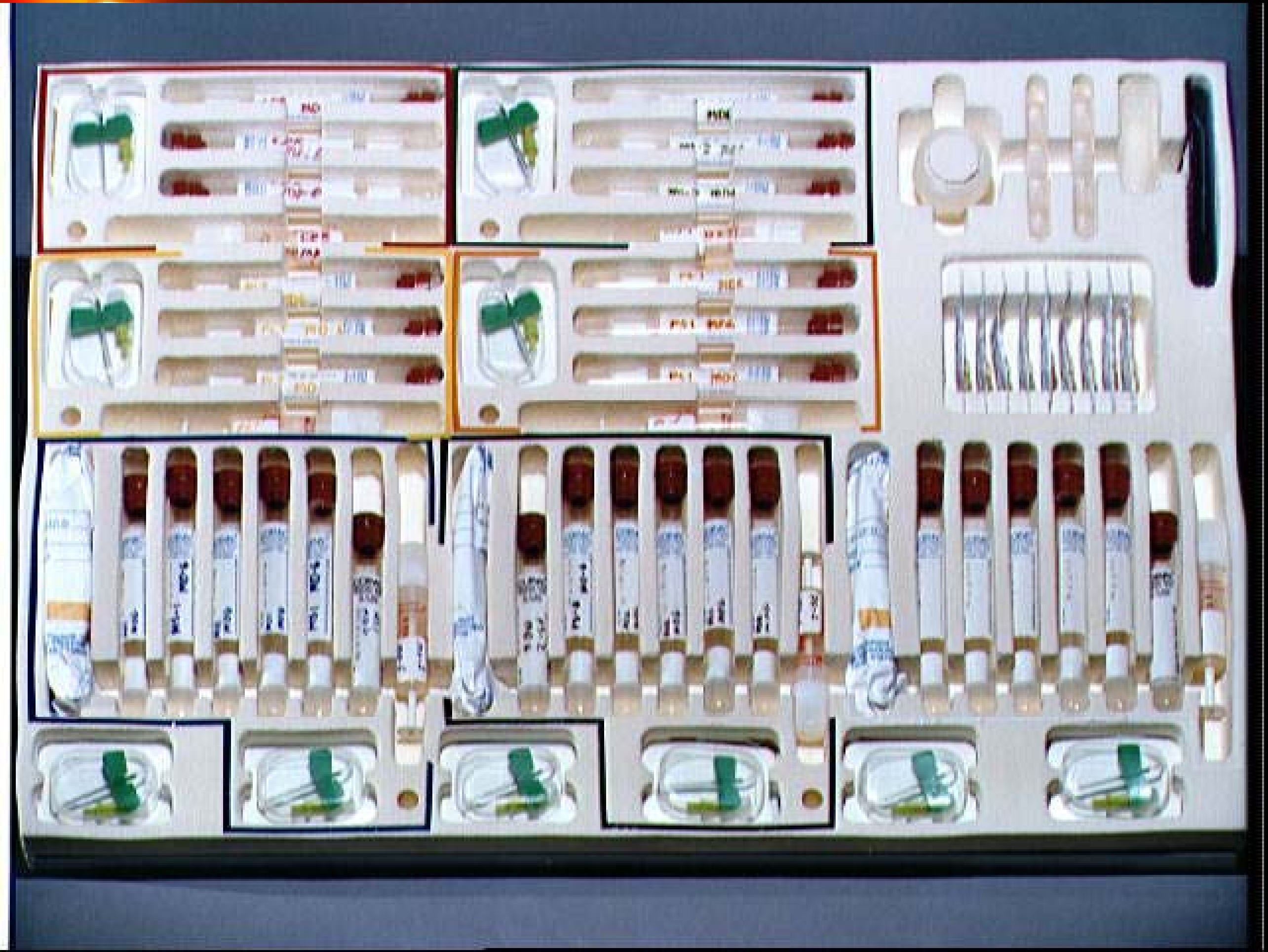
Autoclave

# Limitations of spaceflight experiments:

- Non-invasive methods best
- Non-toxic
- Lightweight and small equipment
- No degassing, explosion or fire risk
- Low power consumption
- Low impact on crew schedule
- N will be small (350 people have flown to space)

# Blood collection kit for Space Lab 1, 1981

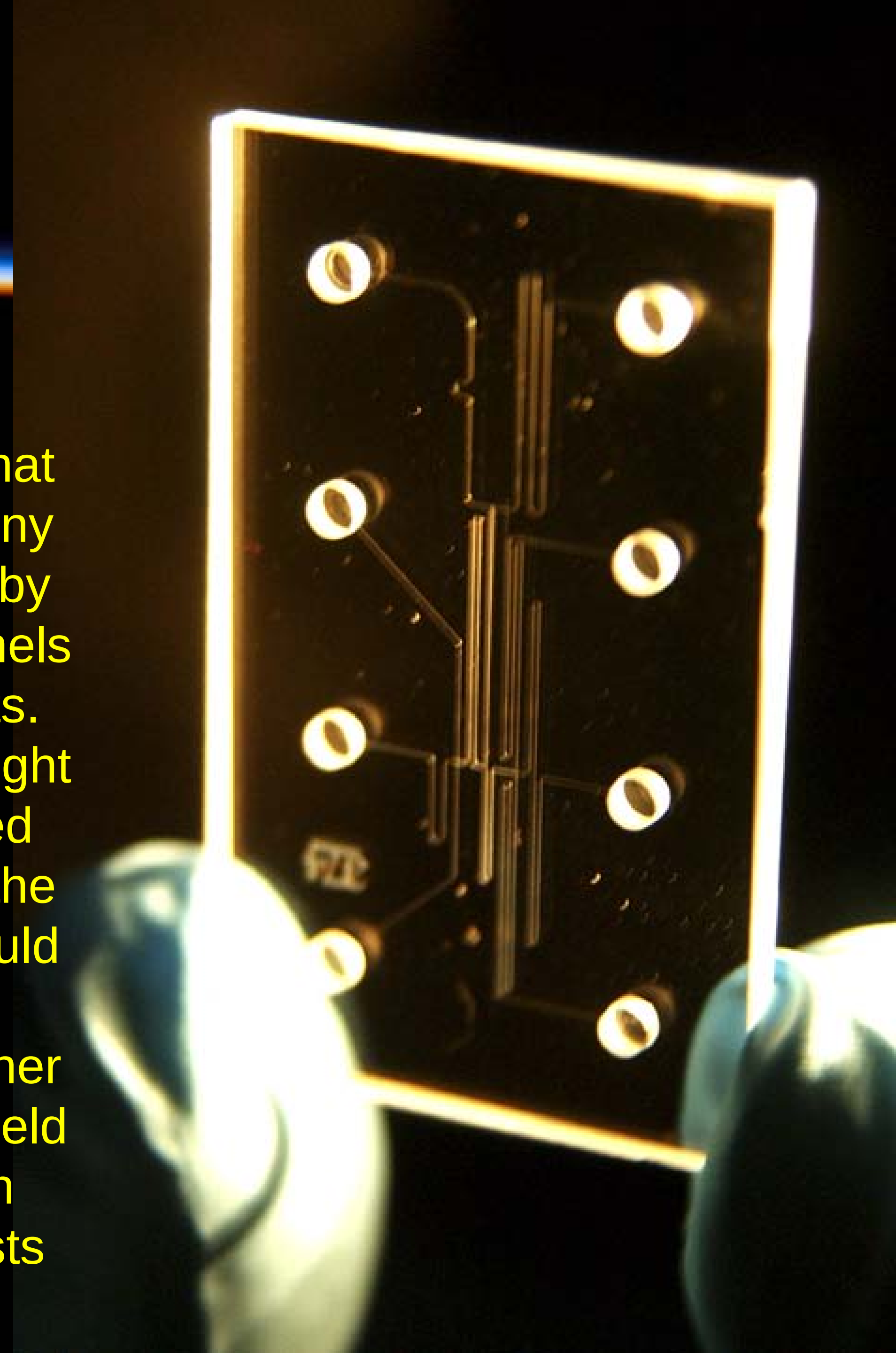


Inside the science module aboard the Earth-orbiting Space Shuttle Columbia, Astronaut David A. Wolf draws blood from payload specialist Martin J. Fettman, DVM. Blood samples from crew members are critical to Life Sciences investigations


ISS013E64639

ISS commander and science officer Leroy Chiao performs an ADUM scan on the eye of flight engineer Salizhan Sharipov Durin during ISS Expedition 10.

The eight holes on this chip are ports that can be filled with fluids or chemicals. Tiny valves control the chemical processes by mixing fluids that move in the tiny channels that look like lines, connecting the ports. Scientists at NASA's Marshall Space Flight Center in Huntsville, Alabama designed this chip to grow biological crystals on the ISS. These chips, the size of dimes, could be loaded on a rover looking for biosignatures of past or present life. Other types of chips could be placed in handheld devices used to **monitor microbes** in water or to quickly conduct medical tests on astronauts. (NASA/MSFC/D.Stoffer)



Before 1988, there were  no countermeasures
except fluid loading and g suits.
Shuttle missions lasted no more than 7 days.
In 1988 Congress approved funds to expand missions to 16 days.
Countermeasure development began in earnest.
Currently, 3 months on the ISS is routine.
Now, we are starting to think about longer duration missions,
and the countermeasures that will be required to
maintain crew health over periods of years.

# NASA Flight Analogs Project models fluid shifts, lack of gravitation force on bone & muscle

- Head-down Tilt Bed Rest
  - serves as a model for studying the physiological changes that occur during spaceflight under controlled conditions;
  - provides a platform for comparison between bed rest and spaceflight;
  - provides a mechanism for testing countermeasures prior to being used in flight.

- 2 weeks of pre-testing
- 30, 60 or 90 days in bed
  - Specimens, samples and testing
- 2 weeks of post testing
- All activities are done in bed
- Standardized diet is consumed
- Sleep/Wake cycle
  - Wake at 0600 hrs
  - Lights out at 2200 hrs

http://www.bedreststudy.com

Pillownaut blogs

# Motion sickness is used to model space motion sickness

The rotating chair is powered by a Neuro Kinetics, Inc. (NKI) 160 ft lb Continuous Torque/320 ft lb Peak Torque servomotor rate table. An integrated low noise mechanical bearing system provides quiet operation with high loads. The chair has a maximum velocity up to 360 degrees/second .

www.graybiel.brandeis.edu/.../facilities.html

# Culture systems are used to measure changes at the cellular level

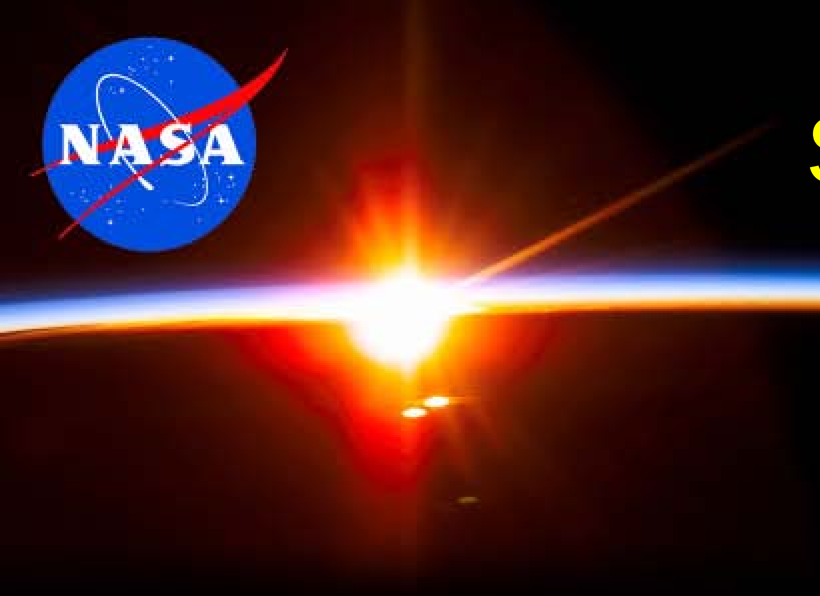
Dr. Cheryl Nickerson is studying the effects of simulated low-g on a well-known pathogen, Salmonella typhimurium, a bacterium that causes two to four million cases of gastrointestinal illness in the United States each year. While most healthy people recover readily, S. typhimurium can kill people with weakened immune systems. Thus, a simple case of food poisoning could disrupt a space mission. Using the NASA rotating-wall bioreactor, Nickerson cultured S. typhimurium in modeled microgravity. Mice infected with the bacterium died an average of three days faster than the control mice, indicating that S. typhimurium's virulence was enhanced by the bioreactor. Earlier research showed that 3 percent of the genes were altered by exposure to the bioreactor.

# Animals can be used as research subjects

STS-65 (1994) Mission Specialist Donald A. Thomas is seen in the spacelab science module making an observation of one of the newts. Smaller organisms, such as the newts, are able to develop from embryos and hatch during the mission as part of an overall program to determine if development occurs normally in the space environment.

# Motion Sickness Treatments

- The 5HT-3 antagonists revolutionized cancer chemotherapy, but are no more effective then placebo for motion-induced illness.
- NASA uses promethazine and scopolamine for treating space motion sickness, but there are side effects.



# Space Motion Sickness: Treatment exacerbates presyncope at landing

People who may have experienced bone loss are at a greater risk of serious injury in a fall.

A side effect of promethazine treatment is orthostatic hypotension and presyncope. Shi, et al, *2010*

# Space Motion Sickness: Treatment leads to sedation?

Promethazine can impair performance to a degree similar to alcohol. Cowings *et al*., 1996

*Research questions:*

Are there other space motion sickness treatments that don't have this side effect?

Is there a countermeasure we can implement?

# Sleep aids: what happens in a night emergency?

Will the crew be groggy and slow to respond?

Will their performance be impaired by the medication?

*Research questions:*

Determine the best sleep aids to use,

that balance efficacy with residual impairment

Test possible emergency antidotes to sleep medications

# Expiration

- Longer duration missions will require extended drug stability.
- NASA has initiated experiments to measure the rate of decay of pharmaceuticals in flight.

# Packaging

- Materials – protect from light, vibration, oxygen, radiation?
- Low bulk
- Low out-gassing
- Oxygen and humidity scavenging
- Usage tracking

| | |
|---|---|
| General NASA info: | http://www.nasa.gov |
| Human Research at NASA: | http://humanresearch.jsc.nasa.gov/ |
| Lab job openings through Wyle: | http://careers.wylelabs.com/ |
| Virginia Wotring | virginia.e.wotring@nasa.gov |