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ANIMAL STUDIES ON SPACELAB-3

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ABSTRACT

The flight of the two squirrel monkeys and 24 rats on Spacelab-3 was the first mission to provide "hands-on" maintenance of animals in a laboratory environment. With few exceptions, the animals grew and behaved normally, were free of chronic stress, and differed from ground controls only for gravity-dependent parameters. One of the monkeys exhibited symptoms of space sickness similar to those observed in humans, which suggests squirrel monkeys may be good models for studying the space-adaptation syndrome. Among the wide variety of parameters measured in the rats, most notable was the dramatic loss of muscle mass and increased fragility of long bones. Other interesting rat findings were those of suppressed interferon production by spleen cells, defective release of growth hormone by somatrophs, possible dissociation of circadian pacemakers, changes in hepatic lipid and carbohydrate metabolism, and hypersensitivity of marrow cells to erythropoietin. These results portend a strong role for animals in identifying and elucidating the physiological and anatomical responses of mammals to microgravity.

INTRODUCTION

With the flight of two squirrel monkeys and 24 rats on Spacelab-3 (SL-3), NASA undertook the first of several missions using animals in a role for which they have long been used in research on Earth — as a model mammalian system with which to delineate the fundamental mechanisms of physiological response to an environment; i.e., microgravity. The primary objective of SL-3 was to evaluate the ability of the Research Animal Holding Facility (RAHF) to maintain animals in a normal, laboratory environment in space. It is important to use an animal that grows normally, behaves normally, and is free from chronic stress because most of the experimental measurements of interest in space are compromised by a subject which does not meet these requirements. Once these criteria are met, a high-quality experimental animal can then be provided for doing high-quality experiments on future missions. Beyond this primary objective, SL-3 did provide the opportunity to obtain preliminary data on animal health and well being in flight as well as to sample selected physiological parameters which might be the focus of future flight experiments.

FLIGHT OPERATIONS

The RAHF is a controlled-environment animal-housing facility, the physical specification and operation of which has been previously described [1]. The RAHF has two interchangeable modules of separate cages that can house up to four squirrel monkeys or 24 rats. Food and water consumption, activity, and intermittent photographic records are obtained automatically. Temperature, humidity, and light cycles can be controlled or varied as desired.

Two adult male squirrel monkeys, free of antibodies to Herpes saimiri, were flown unrestrained. The rats comprised two groups of 12 males each. One group was adults about 12 weeks old; these "large" rats represented the more mature, slower-growing organism. The other group was juveniles about 8 weeks old; these "small" rats represented the younger, faster-growing organism. Four of the large rats were implanted with a transmitter which permitted the continuous monitoring of heat rate and deep-body temperature. Both monkeys and rats were free of several specific pathogens, but were not gnotobiotic or axenic.

The flight animals spent 1 day in the Spacelab prior to launch and 7 days in microgravity and, because of an altered landing site, 6 hours in a jet flight during the return to Kennedy Space Center. Apart from a brief physical examination at 3 hours postflight, data collection could not begin until about 12 hours after landing. The squirrel monkeys were not tested postflight, whereas the rats were sacrificed for a thorough examination. Ground-control rats in cages similar to those in the RAHF (simulation controls) and ground controls in standard vivarium cages were also processed postflight. The ground-control groups could not be subjected to the postlanding jet flight, but were otherwise handled in exactly the same manner as were the flight rats.

RESULTS

Upon completion of the examination of the animals, the following results were recorded.

Squirrel Monkeys

Both squirrel monkeys ate less food, and were less active in space than on the ground (Table 1). Weight loss during the flight was within normal limits (≤ 10 percent). The pattern of food intake indicated that, while one animal maintained relatively normal eating behavior throughout the mission, the other showed abnormally low food consumption for the first 4 days followed by substantial recovery during the last 3 days. Direct measurement of possible sickness episodes was not made. However, there was similarity between the responses of the two flight monkeys with those of monkeys centrifuged at 1.5 g [2]. In the latter case, the centrifuged animals showed frank evidence of sickness during the period of anorexia. Because the food-consumption pattern of one flight monkey was similar to that of centrifuged animals which were observed to be sick, we concluded that the one flight monkey probably experienced symptoms of space-adaptation syndrome during the early days of the flight while the other did not. Videotape records of behavior throughout the flight were consistent with this evaluation. Both monkeys were in good medical condition immediately postflight and no abnormal sequelae were noted thereafter.

Rats

More extensive studies were performed on the rats in the areas of growth, hematology, immunology, blood chemistry, heart rate, body temperature, muscle and bone growth, growth hormone, and liver metabolism. The following findings were recorded.

Growth

As shown in Table 2, the small flight rats grew at the same rate as their control counterparts that were similarly housed on the ground, whereas the larger flight rats grew at a lesser rate than controls. The flight-cage configuration reduced growth rate in both groups, as indicated by the higher body weights

of vivarium control animals at the end of the mission. The weights of various organs (brain, heart, kidney, liver, adrenals, pituitary, spleen, prostate, thymus, parotid, and testes) in flight animals were either not different from simulation-cage control animals or within normal limits of variation [3]. In particular, indications of chronic stress (adrenal hypertrophy, thymic involution, parotid hyperplasia, and liver atrophy) were not observed in either group (data not shown). We concluded that the flight animals grew at a normal rate and that growth-related symptoms of chronic stress were not evident.

Hematology, Immunology, and Blood Chemistry

Hematological indices (Table 3) showed increased hematocrit, red-cell count, and hemoglobin in both groups. Because plasma volume could not be measured, it is unclear whether these changes resulted from increased erythropoiesis or hemoconcentration. However, postflight studies with cultured bone-marrow cells showed that marrow sensitivity to erythropoietin was heightened in the flight animals (Table 4). Production of interferon- γ by spleen cells cultured postflight was dramatically reduced in flight animals (Table 4). Among several plasma-hormones and blood-cell parameters measured postflight, only plasma concentrations of osteocalcin were significantly lower in flight rats (Table 5). However, it is likely that measurement of these relatively labile parameters was compromised by the 12-hour hiatus between landing and sample acquisition. We believe that these measurements, more than the others, are less reflective of any changes which might have occurred during flight.

Heart Rate and Body Temperature

The composite 24-hr heart rate for four rats over the 7-day flight was compared to their heart rate for a similar preflight period. Heart rate was lower in flight at all times of the day, and in particular did not show the increase normally observed during the active period [9]. The period of the rhythm in flight was unchanged from that of preflight (23.9 ± 0.02 hours).

Mean body temperature was not affected by the flight, but the period of its rhythm was increased to 24.4 ± 0.3 hours. The finding suggests the possibility that microgravity might cause the body-temperature rhythm to become free-running. If so, it might then dissociate from that of heart rate, which did not show an indication of becoming free-running.

Muscle

Both large and small flight rats had reduced mass of selected hind-limb extensor and flexor muscles postflight (Table 6) when compared to similar control rats. The two groups differed in that the large control rats lost muscle mass from their preflight values, whereas most of the muscles in the small control animals showed some growth despite the obvious cage effect. In view of this, the muscle mass loss in flight was more pronounced for the small, faster-growing rats than for the more mature, slower-growing ones. The antigravity soleus muscle was the most sensitive to microgravity, with the less-gravity-dependent tibialis anterior the least.

Histochemical and morphological analyses [10] showed that loss of mass was apparently due to cell shrinkage rather than necrosis. However, about 1 percent of flight fibers were necrotic and up to 70 percent of solei fibers had core lesions. Diaminopeptidase activity was unchanged, but both triaminopeptidase and Ca-activated protease activity were substantially increased in flight muscles. A decrease in mitochondrial NADH dehydrogenase activity, a marker of aerobic metabolism, coupled with increased glycerophosphate dehydrogenase, a marker of glycolysis, suggested a shift from aerobic to glycolytic metabolism in flight muscles. Fast fiber types appeared more numerous in flight than in control solei and fast myofibrillar ATPase activity was elevated in flight muscles.

Biochemical analyses of muscles (Table 7) from small animals showed that loss of protein, probably from myofibrils, corresponded to loss of muscle mass. Tyrosine content, an indicator of protein catabolism, was elevated only in small solei while the ratio of glutamine to glutamate, another such indicator was increased in most of the flight muscles. Glycogen deposition was observed in all flight muscles, suggesting a systemic effect apart from differences in muscle mass changes or metabolic changes specific to the individual muscles.

Bone

Growth of tibial plates from small rats was reduced in flight (Table 8) and the effect was consistent in all three zones of the plates. Using two injections of calcein as a marker, the rate of periosteal bone formation in the tibial diaphyses of large rats was 66 percent of preflight values for flight rats when compared to simulation cage control rats [14]. There were no differences between flight and control proximal humerus of large rats for the following parameters: percent trabecular bone volume, percent osteoclast surface, percent osteoblast surface, number of osteoblasts for osteoclasts per millimeter, and longitudinal bone growth [14]. There was a substantial increase in fragility based on biomechanical measurements (Table 9). This increased fragility occurred despite the fact that there were no differences in calcium, phosphorus, or hydroxyproline content of either trabecular or cortical bone [8, 15]. But in the absence of gross demineralization of long bones, gradient-density analysis showed that there was a shift in mineral concentration from lower specific-gravity fractions (1.3-1.7, 1.8-1.9) toward higher-density fractions (2.0-2.1, 2.2-2.9) in the flight bones [15]. Histochemical analyses of osteoblasts and osteoclasts showed no difference between flight and control animals for the following parameters: alkaline and acid phosphatases, golgi activity, secretory granule size, dipeptidyl peptidase, and lysosomal activities [16].

Vertebral bone differed somewhat from long bones in that mass was decreased in the absence of demineralization (Table 10). Of particular interest was the fact that bone osteocalcin concentration was lower in flight animals. There was no difference between flight and control vertebrae of small or large rats for the following parameters: percent trabecular bone volume, percent osteoblast or osteoclast surface, osteoblasts or osteoclasts per millimeter of bone, and longitudinal bone growth.

Growth Hormone

Culture of pituitary somatotrophs [17] showed that the number of somatotrophs was increased and that their growth hormone content was higher in flight rats (Table 11). However, when growth hormones are implanted into hypophysectomized rats, release of hormone from flight cells was decreased as indicated by tibial growth. This apparent defect in the release of growth hormone thus caused total synthesis by somatotrophs from flight rats to be substantially lower than that in control rats. There was no difference in hormone species between flight and control animals. If growth hormone release was reduced during flight, it might have caused some of the changes in muscle and bone previously observed.

Liver Metabolism

Flight animals apparently had an increase in carbohydrate-based metabolism, suggested by the 20-fold increase in glycogen content, and a decrease in lipid-based metabolism, as suggested by the decreased cholesterol content (Table 12). The latter may have resulted from the decrease in activity of HMG-CoA reductase, which is the rate-limiting step in cholesterol synthesis. While sphingomyelin content was not different, the rate-limiting enzyme for sphingolipid synthesis, serine palmitoyl transferase, was lower in flight animals. The absence of any differences for the amino transferases suggests that the absence of whole-body catabolic activity and that protein catabolism which occurred in specific organs

(e.g., muscle) was isolated to those organs. Tyrosine aminotransferase is particularly sensitive to circulating glyccorticoids. The lack of an increase in its activity is a further indication of minimal chronic stress in the flight animals.

Other Observations

Electron microscopic analysis of otoconia showed no degeneration of macular cells or demineralization of otoconial masses in flight rats [20]. Neurohistochemistry indicated no increase in cytochrome oxidase activity in the paraventricular nucleus, the site of control of fluid balance [21]. An extensive analysis of receptor binding in various parts of the brain (hippocampus, prefrontal cortex, lateral frontal cortex, posterior cortex, amygdala, pons-medulla, and cerebellum) showed only an increase in hippocampal binding for 5-hydroxytryptamine (5HT) [22]. However, membrane Mg-dependent NA-K ATPase activity was lower in flight rats.

There was no change in kidney receptor affinity for $1, 25\text{-OH})_2$ Vitamin D_3 , suggesting that the kidney was not the site of control of any changes in calcium excretion [23]. Histomorphological analysis of cardiac muscle showed increased glycogen and lipid deposition in flight rats and loss of microtubules as compared to controls [24]. Histochemical and morphological analyses of parotid salivary gland showed no hyperplasia or major enzyme changes indicative of chronic discharge of the sympathetic nervous system [25].

CONCLUSIONS

The data presented in the previous sections indicate that the RAHF was able to maintain both rats and monkeys in a relatively normal condition suitable for their use as experimental animals. Growth parameters and several indices of chronic stress suggested that changes in bone and muscle were a result of exposure to microgravity per se and not an artifact resulting from adverse housing conditions. For the most part, changes in hematology, muscle, and bone were qualitatively similar to those reported in humans and in animals from the Kosmos flights of the Soviet Union. However, it is apparent that microgravity induces a wide range of physiological changes, some of which have not been measured heretofore. Further evaluation of these parameters will require more flight experiments, including collection of samples in flight to eliminate the complications resulting from delayed postflight sampling.

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Table 1. Food consumption and weight change of squirrel monkeys.

	WEIGHT (G)	% WT. LOSS	FOOD CONSUMPTION (% PRE-FLIGHT)	ACTIVITY (% PRE-FLIGHT)
M1	942	3	67	44
M2	962	8	20	11

Table 2. Weight change of rats (Ref. 3).

	RAIS	
	"SMALL"	"LARGE"
PREFLIGHT	200.1 ± 1.5 ^A	382.3 ± 6.5
FLIGHT	242.9 ± 3.1	385.9 ± 4.6 ^B
CONTROL (SIMULATION CAGE)	258.2 ± 4.1	400.8 ± 7.8
CONTROL (VIVARIUM CAGE)	301.8 ± 5.0 ^B	433.0 ± 5.0 ^B

^A $\bar{x} \pm$ S.E.M., N = 12

^B DIFFERENT FROM CONTROL (SIMULATION CAGE), P < .05 OR LESS

Table 3. Hematology of rats (Ref. 4).

	CONTROL	FLIGHT
HEMATOCRIT, %	40.7 ± 1.50 ^A	43.6 ± 1.30 ^B
RBC, 10 ¹² /L	5.85 ± .28	6.46 ± .40 ^B
Hb, G/DL	13.5 ± .5	14.7 ± .60 ^B
MCV, FL	69.70 ± 2.20	67.80 ± 3.50
MCH, PG	23.10 ± 1.02	22.8 ± 1.22
MCHC, G/DL	33.10 ± .55	33.6 ± 1.51
WBC, 10 ⁹ /L	7.89 ± 2.0	7.88 ± 1.8
DIFFERENTIAL, %		
LYMPHOCYTES	89.5 ± 2.0	77.8 ± 8.4 ^B
MONOCYTES	1.2 ± 0.9	1.6 ± 1.1
EOSINOPHILS	0.9 ± 0.7	0.9 ± 1.0
NEUTROPHILS	8.2 ± 4.3	19.7 ± 7.9 ^B

NO DIFFERENCE FOR SPLEEN CELL OR BONE MARROW DIFFERENTIAL COUNTS

^A $\bar{x} \pm$ S.E.M., N = 12

^B P < .001

Table 4. Interferon-gamma production by cultured spleen cells (Ref. 5) and sensitivity of bone-marrow cultures to erythropoietin (Ref. 4) in rats.

	CONTROL	FLIGHT
NO. SPLEENS PRODUCING INTERFERON- γ NO. SAMPLES	7/10	1/10 ^A
BONE ERYTHROID COLONIES/10 ⁵ CELLS		
DAY 3, .02 U EP/ML	2.67 ± 2.13 ^B	22.7 ± 2.54 ^C
1.0 U EP/ML	7.67 ± 2.89	32.8 ± 7.32 ^C
DAY 6, .02 U EP/ML	.583 ± .319	4.06 ± 1.68 ^C
1.0 U EP/ML	1.83 ± .43	8.67 ± 3.04 ^C

^A NEARLY UNDETECTABLE PRODUCTION OF INTERFERON

^B $\bar{x} \pm$ S.E.M., N = 8

^C P < .001 OR LESS

Table 5. Plasma measurements in rats (Ref. 3, 4, and 6-8).

	N	SIM CONTROL	FLIGHT
CALCIUM, MG/DL	12	9.98 ± .64 ^A	9.00 ± .16
PHOSPHORUS, MG/DL	12	10.4 ± .44	10.1 ± .26
CREATININE, MG/DL	12	1.12 ± .16	1.02 ± .04
ALKALINE PHOSPHATASE, IU/L	12	198 ± 12	212 ± 19
OSTEOCALCIN, NG/ML	6	347 ± 12	271 ± 25 ^B
1, 25- DIHYDROXY VIT. D3, PG/ML	6	64 ± 6.2	94 ± 17
CORTICOSTERONE, UG/DL	6	17.0 ± 3.0	17.7 ± 4.4
THYROXIN, UG/DL	12	8.8 ± 0.9	9.1 ± 1.0
TRIIODOTHYRONINE, NG/DL	12	79.1 ± 8.8	72.6 ± 6.1
GROWTH HORMONE, NG/ML	12	7.5 ± 2.9	7.2 ± 5.1
PROLACTIN, NG/ML	12	2.8 ± 0.9	3.5 ± 6.1
ERYTHROPOIETIN, NM/ML	6	19.0 ± 3.7	16.5 ± 4.6
ATRIOPEPTIN, NG/ML	6	2.80 ± .48	2.00 ± .67
RENIN, NG/ML	6	44.2 ± 7.3	35.6 ± 6.6

^A $\bar{x} \pm$ S.E.M.

^B P < .01 OR LESS

Table 6. Muscle weights (G/100 G body weight) of rats expressed as percentage of preflight values (Ref. 3).

	CONTROL	FLIGHT
SMALL		
SOLEUS	0.0 ^A	-32.5 ^B
GASTROCNEMIUS	+ 7.9	- 9.7
PLANTARIS	+ 8.7	-10.6 ^B
TIBIALIS ANTERIOR	+ 1.0	- 4.6
EXTENSOR DIGITORUM LONGUS	+ 4.5	- 6.8 ^B
ADDUCTOR LONGUS	- 4.3	0.0 ^B
LARGE		
SOLEUS	- 2.2	-20.0 ^B
GASTROCNEMIUS	- 4.4	-13.9 ^B
PLANTARIS	- 6.0	-12.0 ^B
TIBIALIS ANTERIOR	- 6.0	-11.0
EXTENSOR DIGITORUM LONGUS	- 4.2	-10.6 ^B
ADDUCTOR LONGUS ^C	-15.3	-15.3

^A MEAN WEIGHT/100 G BODY WEIGHT EXPRESSED AS PERCENTAGE CHANGE FROM PREFLIGHT, N=12

^B P < .05 OR LESS

^C PREFLIGHT VALUES UNUSUALLY HIGH

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Table 7. Biochemical measurements in muscles of small rats expressed as percentage of control (Refs. 11 and 12).

	SOLEUS	GASTROC.	PLANTARIS	EX. DIG- LONGUS	TIBIALIS ANTERIOR
PROTEIN	- 34 ^A	- 13	- 17	- 17	- 6
GLYCOGEN	+144	+ 89	+ 61	+ 63	+ 53
TYROSINE	+ 37	NS ^B	NS	NS	NS
GLUTAMINE	- 20	- 20	- 24	- 21	NS
GLUTAMATE	- 56	- 46	- 42	- 26	- 42
RATIO GLN/GLU	+ 79	+ 48	+ 29	NS	+ 39
ASPARTATE & ASPARTAMINE	- 77	NS	- 11	NS	NS
MALATE	- 60	- 34	NS	NS	NS
ALANINE	- 21	NS	NS	NS	NS

^A NUMERICAL VALUES SIGNIFICANT AT P < .05 OR LESS

^B NOT SIGNIFICANT

Table 8. Height in millimeters of tibial-growth plates of small rats (magnification in parentheses) (Ref. 13).

	TOTAL (X111)	RESTING (X444)	PROLIFERATIVE (X444)	HYPERTROPHIC/ CALCIFYING (X444)
CONTROL	59.15 ^A ± 1.30	10.08 ± .67	16.76 ± .82	33.19 ± 1.22
FLIGHT	50.59 ^B ± 1.55	9.04 ^B ± .60	15.42 ^B ± .78	25.82 ^B ± 1.47

^A $\bar{x} \pm$ S.E.M., N = 6

^B P < .01 OR LESS

Table 9. Biomechanical measurements on humeri of small rats (Ref. 8).

	SIM. CONTROL	FLIGHT
ULTIMATE LOAD, NEWTONS	41.5 ± 1.54 ^A	29.8 ± 1.76 ^B
ULTIMATE DEFORMATION, MM	.677 ± .017	.575 ± .039
WORK TO ULTIMATE LOAD, N/MM	16.1 ± .81	8.86 ± 1.18 ^B
INITIAL STIFFNESS, N/MM	95.4 ± 5.57	70.5 ± 4.08 ^B

^A $\bar{x} \pm$ S.E.M., N = 6

^B FLIGHT DIFFERENT FROM CONTROL AT P < .001 OR LESS

Table 10. Analyses on vertebra L3 of small rats (Ref. 8).

	CONTROL	FLIGHT
DRY WEIGHT, MG/G BODY WEIGHT	.354 ± .009 ^A	.318 ± .018 ^B
CALCIUM, UG/MG BONE	180 ± 13	179 ± 3.7
OSTEOCALCIN, UG/MG BONE	2.43 ± .11	2.19 ± .22 ^B

^A $\bar{x} \pm$ S.E.M., N = 6

^B P < .01

Table 11. Analyses of cultured pituitary somatotrophs (Ref. 17).

	CONTROL	FLIGHT
SMALL		
% SOMATOTROPHS/PITUITARY	42.5	44.0
% PRL CELLS/PITUITARY	33.5	31.8
MG STH/10 ³ SOMATOTROPHS	21.6	33.3 ^B
MG STH RELEASED/10 ³ SOMATOTROPHS	108.6	60.7 ^B
NET SYNTHESIS/6 DAYS, MG/STH/10 ³ SOMATOTROPHS	90.0	35.3 ^B
LARGE		
% SOMATOTROPHS/PITUITARY	36.7	43.7 ^B
% PRL CELLS/PITUITARY	37.6	33.4
MG STH/10 ³ SOMATOTROPHS	36.9	67.1 ^B
MG STH RELEASED/10 ³ SOMATOTROPHS	126.4	94.5 ^B
NET SYNTHESIS/6 DAYS, MG/10 ³ SOMATOTROPHS	94.6	41.9 ^B

^A \bar{x} ONLY, N = 8

^B P < .05 OR LESS

Table 12. Biochemical analyses of liver from small rats (Refs. 18 and 19).

	CONTROL	FLIGHT
LIVER WEIGHT, G	11.1 ± 0.3 ^A	9.9 ± 0.5
MICROSOMAL PROTEIN, MG/G LIVER	5.6 ± 0.3	4.2 ± 0.3 ^B
GLYCOGEN, MG/G LIVER	1.24 ± .98	24.5 ± 9.8 ^B
CHOLESTEROL, UMOL/G LIVER	9.1 ± 1.0	6.9 ± 0.4 ^B
PHOSPHOLIPIDS, UMOL/G LIVER	35.8 ± 1.5	52.3 ± 1.7
SPHINGOLIPIDS, UMOL/G LIVER	2.6 ± 0.2	2.3 ± 0.2
P450, NMOL/MG PROTEIN	5.38 ± 1.23	1.71 ± 0.35 ^B
B5	0.71 ± .30	0.62 ± .32
ENZYMES:		
LIGASE, NMOL/MIN/MG PROTEIN	39.9 ± 2.0	54.5 ± 9.6 ^B
SERINE PALMITOYL TRANSFERASE, NMOL/MIN/MG PROTEIN	29.0 ± 2.7	17.4 ± 2.1 ^B
GLYCEROL-3-PHOSPHATE ACYLTRANSFERASE, NMOL/MIN/MG PROTEIN	1.06 ± .14	1.00 ± .24
HMG-COA REDUCTASE, NMOL/MIN/MG PROTEIN	8.6 ± 1.3	1.7 ± 0.3 ^B
TYROSINE AMINO TRANSFERASE, UMOL/MIN/MG PROTEIN	.021 ± .007	.026 ± .005
ASPARTATE AMINOTRANSFERASE, UMOL/MIN/MG PROTEIN	1.50 ± .24	1.49 ± .19
GLUTATHIONE-S-TRANSFERASE, UMOL/MIN/MG PROTEIN	11.5 ± 0.8	11.1 ± 2.8

^A $\bar{x} \pm$ S.E.M., N = 6

^B P < .05 OR LESS

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