FINAL REPORT TO

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

Research Grant NsG-515

Monitoring Brain Function and Performance in the Primate Under Prolonged Weightlessness.

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This report is issued in compliance with the terms of the above contract as a summarizing statement of the work accomplished during the term of the Contract.

SUMMARY

Our original statement of proposed work indicated in outline the neurophysiological correlates which might be found indicative of physiological as well as psychological states. Not only are these correlates indicative of the "steady state" condition, but they are also sensitive criteria for the determination of changes in state. The use of computer analysis for the evaluation of the electroencephalogram has been developed in this laboratory to study a broad gamut of physiological states in the mammalian organism. These have included extensive analyses of sleep states as well as the alert, highly-oriented and goal directed behavior exhibited by animals in a performance task situation. It was the purpose of the work undertaken in this contract to establish by systematic study the role of environmental stimuli in determining central nervous processes. The fundamental information obtained from these studies would then serve as criteria for the evaluation of changes occurring in the central nervous system of a primate exposed to a weightless environment for prolonged periods.

The effects of proprioceptive and vestibular inputs interacting with visual cues are well known in establishing stable posture and spatial orientation. Because of its relatively clear anatomical organization as well as substantial knowledge of its arrangement in information processing, this particular mechanism was chosen to serve as the nucleus around which our studies in proprioception would be formulated. Intensive preparations were initiated to provide experimental animals as well as apparatus necessary to collect neurophysiological data from monkeys manipulated in ways to directly influence the mechanisms involved in visuomotor co-ordination, orientation and posture. This laboratory has long been engaged in the study of EEG correlated of behavior that might be brought to bear on assessment of the capability of the animal to perform discriminative and coordinated tasks. Experimental paradigms have been designed to accomplish these purposes with appropriate sensitivity.

This program will form the scientific basis for the Biosatellite experiments in the study of the effects of weightlessness on the mammalian organism, with special emphasis on the effects of protracted exposure.

Recognizing that the mammalian organism is highly complex with many subsystems acting synergistically to maintain the whole, as many physiological parameters as possible are being monitored with a range of techniques in many instances in the forefront of current states of the art. These parameters will serve as controls and as indicators of alterations in the global state of the animal, thus taking account of body systems peripheral to the particular one under study. The physiological variables considered are: systemic and peripheral arterial blood pressure, venous blood pressure, brain PO_2, intracranial pressure, GSR, heart rate, respiration, muscle tone, eye movements, and reflexes in addition to the many recordings made from various cortical and subcortical structures in the brain. These parameters will also be supported by various behavioral measures estimated by means of a visuomotor coordination and oddity discrimination tasks, as well as tasks which will assess short-term and long-term memory. An evaluation of the behavioral performance is expected to reveal such alterations in state as will be produced by a stressful environment and distracting events. To provide one further criterion for the assessment of stress levels, evaluations will be made of the urinary corticosteroid output, and to evaluate transient stress phenomenon, similar biochemical assays may be made in blood.

RESEARCH ACCOMPLISHMENT

Studies relating to the influence of proprioceptive mechanisms have been conducted in a highly sophisticated experiment concerned exclusively with this question. Animals which were specifically prepared by sectioning the VIII nerve bilaterally to remove vestibular sensibility, then vibrated on an industrial shake table while recordings were made of the EEG in surface and deep brain structures. Since it was planned to subject the data to computer analysis, precise measurements of accelerations of the animals' head and torso and the table were also made. The head acceleration was measured in three planes to establish directional dependencies, if any. Six animals were prepared, three with the nerves sectioned and three normals.

The six animals were subjected to vibrations which swept up and down in frequency from 5 cps to 40 cps with a short resting period between sweeps. The amplitude of the vibrations was a constant displacement of 0.25 inches peak to peak from 5 cps to approximately 13 cps where this displacement produced a 2G peak acceleration. The remaining portion of the swept spectrum was then run at a constant 2G peak acceleration. All animals were run blindfolded to minimize central nervous effects, including "photic driving", from rhythmic visual inputs.

The EEG were recorded from brain stem structures, as well as from allocortical and neocortical areas. All data were recorded on paper and magnetic tape.

Although all of the data collected in the experiment have not yet been analyzed, a partial analysis of the data has shown a definite dependency of the EEG in central brain structures on vestibular input. The vestibular and proprioceptive inputs resulting from the whole body vibration appear to have mutual influence on the EEG. Sectioned animals seem to exhibit a greater EEG driving in synchrony with the vibratory input than the unsectioned animals in midbrain and thalamic structures. The implications of these findings are, of course, very broad, since augmented responsiveness occurs here in regions vitally concerned in basic mechanisms of consciousness and alerted behavior.

Hasty conclusions must be avoided on limited experimental evidence, but an obvious hypothesis certainly warrants further study. If the vestibular mechanism plays a modulating role which modifies the proprioceptive response to the same environmental input, then an environment which perturbs vestibular functions will probably alter aspects of brain integrative capability. The disturbance may not necessarily be entirely disruptive. In the weightless state, removal of vestibular influence may have an advantageous effect on the decreased proprioceptive input.

A behavioral performance task has been designed which is expected to provide an assessment of the aspects of CNS function which relates to visuomotor coordination, discriminatory ability and memory. The choice of these areas of primary interest was necessarily dictated by the limitations imposed by the vehicle which has been made available for this experiment. Implementations of the tests is through a device which houses two basic tasks. A drawing of this device is included in the appendices. Visuomotor coordination will be tested by means of two concentric discs which rotate in the same direction but at slightly different speeds. The disc nearest the animal will have a hole cut in its periphery while the back disc will have a push button switch mounted in its periphery. The radii of switch and hole will be identical so that when they are coincident, the switch is available to the animal. Since the discs rotate at slightly different speeds, the precession will cause the manipulanda to be coincident with the hole at different points of the circular path. The animal is thus required to visually track the switch and the hole simultaneously and then make a highly coordinated movement at the appropriate time to operate the switch. Two successful tries are rewarded with a food pellet.

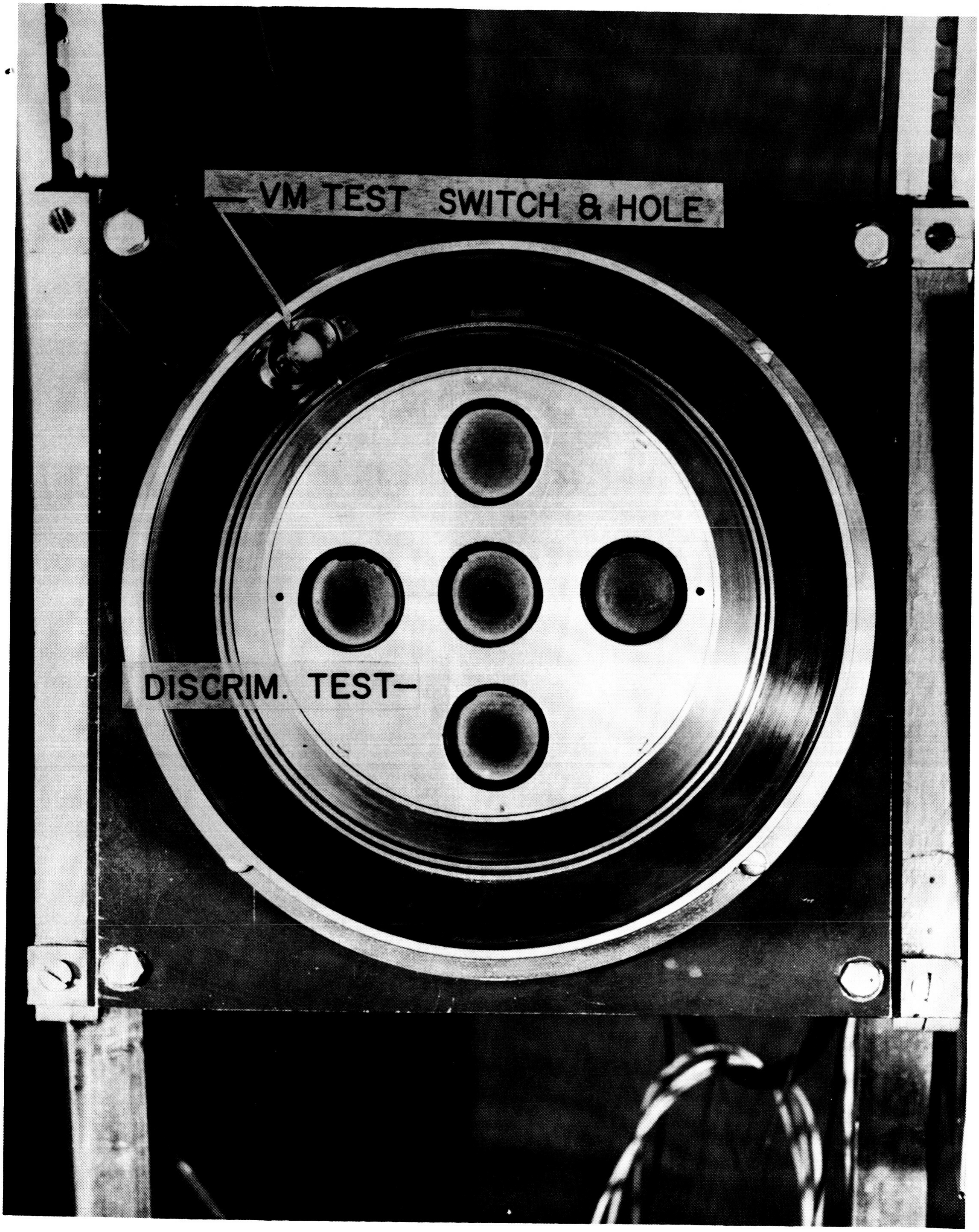
Early trials with this device have indicated that a normal animal can successfully perform this task at very high speeds of rotation. Speeds of 80 rpm during which the opportunity to operate the switch lasts for only 1.5 seconds appear to be well within the capability of the animal. The animal's ability to perform the task at these speeds is most desirable since it is indicative of a very sensitive way in which to study decrements in visuomotor coordinations.

The short term memory and discrimination task is the typical delayed-match-to-sample performance situation. Located centrally in the behavioral tester, illustrated in the appendices, are five glow discharge tubes. The tubes have been manufactured specifically for this purpose by the use of symbols in place of the usual numerals. These tubes are arranged with four peripheral units and one central and are located behind transparent windows which serve as switch plates. The animal's response in this test requires pressing "at" the symbol behind the window. The task itself is pre-programmed through the behavioral logic in the following sequence. One of the four possible symbols is selected randomly by the logic and displayed in the central window. When the animal presses that window, the symbol is removed for a predetermined length of time. At the end of time out, the selected symbol is again displayed in one of the four peripheral windows, while simultaneously, other symbols appear in the remaining three windows. The successful response to this task is to operate the switch plate over the "correct" symbol. The animal is thus required to remember and discriminate the correct symbol. Two successful operations result in an opportunity to obtain a food pellet.

Preliminary tests with animals working in this particular paradigm have indicated a critical characteristic for the delay period. The animals display indecisiveness manifested by rapid movements of their hands over several of the windows without producing enough force to operate the switch. When the choice has been reduced to two symbols, the subjects will place one hand on each window and finally press one. If the feeder relay does not then make the appropriate reinforcing sound, indicating a correct response, the animal will respond within milliseconds by pressing another window with the other hand. This task is expected to be particularly adapted to the investigation of CNS function as an indicator of the ability of the animal to perform a complex discrimination substantially more difficult than simple symbol identification.

Both of these behavioral tasks will be evaluated in the laboratory under various stressful states artificailly induced to simulate the anticipated conditions of protracted space flight. Decrements in performance and their concomitant changes in the EEG patterns will be studied under the effects of sleep deprivation, distraction, shifts in test parameters, food deprivation, and the influence of some drugs known to produce disorientation. Such studies will form the baselines against which the data collected during the actual flight will be evaluated.

Quite aside from the aspects of a single experiment in space, this study is also expected to contribute significantly to basic knowledge in the areas of learning and behavior.


VM TEST SWITCH & HOLE
DISCRIM. TEST-

Appendix II

Summary of Results

Monkey Centrifuge and Spin
Simulated Launch and Insertion-spin
Acceleration Profiles

Biosatellite space craft launch, stabilization and insertion into orbit profile

Tests conducted at USC centrifuge facility 12/11/63

This preliminary report summarizes the results of an experiment conducted during the NASA-Ames series of tests at the USC facility. We are indebted to the Ames group for allowing us to slip into their schedule an experiment using an implanted monkey N-6 (Pluto). The primary objectives of this experiment were threefold, first to test the feasibility of obtaining EEG during this test, second the effects of this type of stress on the EEG, and thirdly, to test the desirability of the eye balls out (EBO) position in a proposed launch profile.

The results presented in this report indicate a need for several more experiments of this nature to be carried out within the confines of a relatively limited scope of objectives, with the prime objective of establishing base line information for this particular phase of the entire biosatellite program.

These results also demonstrate that the ever present influence of the 1G environment may still prevent an adequate simulation of the actual course of events in the weightless state. This compounding of the simulation problem seems to be heightened by the need for the 100 rpm stabilization spin. In this regard, the EBO configuration for launch appears to be only a questionable second best solution. In spite of the complex and highly stressful gyrations, recording EEG from implanted electrodes has once again proven to be a practical, significant, and safe physiological monitoring technique.

1. Gross observations made at the time of the experiment may be summarized as follows:
    a. The animal appeared to be unaffected by the situation prior to the run. He remained very tractable and was easily handled. He sat comfortably in the chair and offered little objection to the restraint. However, he did chew frequently on some adhesive tape and webbing lying within reach.

b. Discomfort was displayed when the animal had been placed in the face down position. However, there were no indications of violent efforts to free himself from the restraint.

c. The animal appeared to withstand up to 6g without any indication of stress. However, at about 8g a swelling of the lower eye lids became noticeable. At about 10g there was a flaccidity of the lips and by the 11g both lids have swelled to the point where the eyes were closed by the swelling. Immediately after the end of the run, the animal appeared dazed and unable to respond to auditory or visual stimuli. He would not accept food. Within a few minutes, however, he accepted food, had pupillary responses, responded to clicks and appeared weakened but not injured.

d. Within 15 to 20 minutes after the run, the animal when supported in a standing position on the floor appeared weak in the legs and showed a desire to lie on the floor. When moved along the floor in a standing position with his feet touching the floor, he was unable to make coordinated walking movements. When moved backward, however, he seemed to be able to coordinate the movement of his legs.

e. After the walking tests, the animal was placed in his cage and presented with fruit which he ate with normal vigor and appetite. His feeding habits appeared to be normal in every respect including the peeling of the fruit before eating. His arms, hands and jaw seemed to be functioning at or near the muscular tonus normally observed.

2. Extensive sub-conjunctival bleeding and blood in the anterior chamber of the eyes was noted. There were indications of bleeding from the nose;, apparently from the Kiesselbach's area. The findings clearly indicate that the animal would be unable to see any form of visual presentation for some time after exposure to the profile.

3. X-rays show no displacement of the depth electrodes. Previous histological examination of one of our animals centrifuged at the General Electric facility on the same centrifuge-spin profile has demonstrated that no electrode movements had taken place which could cause tissue damage.

4. A page referenced, running commentary obtained during the test, is also included to provide a general time course of events picture. The EEG machine and the tape recorder were operated continuously during the entire run. Recordings were made of the EEG from screws located over the left visual cortex, and bipolar depth electrodes located in the right amygdala, right hippocampus and the right midbrain reticular formation. The EKG was also recorded. All voice comments were recorded on a direct channel. The voice annotation proved very useful in establishing reference points while viewing the motion picture films made during the tests. In future experiments, however, we would hope to establish better timing coordination with an indicator on the animal frame to synchronize the commentary and paper record with the film.

5. The three EEG plates were made up of sections of record selected for their relevance to particular events. The notations on the plates are self-explanatory but a few things should be pointed out. Figure 1A has been marked at the point at which the centrifuge and the camera are started. A noticeable artifact is introduced by the camera motor due to an unfortunate placement of the EEG cables near the camera motor housing. However, the significance of the data was not impaired. The EEG findings clearly reveal extreme arousal in the initial phases of the centrifuging, with increased amplitude in both slow and fast EEG components. Note the onset of large amplitude (100 uv) slow 1 cps activity which becomes prominent in the visual cortex leads and then apparent in the other leads as the centrifuge begins to approach the full G load. The EKG was obliterated by the high amplitude EMG (from struggling), as well as blocking of the EKG amplifier by excessively large transient voltage peaks. It has been impossible to assess the heart

rate during certain critical phases of these tests as a result of the excessive masking of the EKG. It is unlikely that any other system of electrocardiographic recording would overcome this basic defect of inherent interference from electromyographic activity in the struggling or straining subject.

In Plate 2, typical records have been selected from the coasting spin phase of the run. During the coasting period, a pronounced cardiac arrythmia appeared, accompanied by bursts of very high amplitude 6 cps activity in all EEG leads. It may be emphasized that this abnormal EEG was most frequently seen to precede the onset of arrythmia implying some form of Cns influence on heart action. This particular finding is one which we are most interested in pursuing in future experimentation of this type. The spin-up phase (Plate 2B) induced very large amplitude waves in the frequency range of 4 to 6 cps in the visual cortex. No further study has yet been attempted to relate these waves to the rate of rotation, but these waves may be due to some form of visual input. The spikes seen in the visual cortex and amygdala in Plate 2C are definitely abnormal and appear as the centrifuge approaches 5.5g during the spin phase. With the centrifuge stopped while the spin continues, the spike like character of the EEG persists. In general form, the EEG is different during the spin phase from any other phase of the test. Also noted during this phase of the tests was an almost sinusoidal rhythmicity in the EKG lead during centrifugation and spin, which corresponded precisely with the rotation rate. This finding appears to be indicative of a very important factor, if the electrodes were moving relative to the skin to produce the artifactual voltage, there must have existed some rather large forces which can be classified essentially as vibratory. This conclusion is based on the rather complex motions of the G vector during this particular phase. An exact analysis of the G vector orientation at various points on the animal may be a valuable bit of information since this simulation experiment cannot eliminate the effects of gravity. The effects of the imposed G loading during the spin phase cannot be readily assessed under these conditions because neither of these two factors taken alone seem to produce the same effect. The role of the earth's gravitation in this test, may thus assume significant proportions.

The post-spin phase showed a record very like the pre-test record, except that all leads had bursts of high frequencies (16-20 cps) with occasional spiking in the visual cortex and the midbrain reticular formation (Plate 3). There was a general decrease of activity in the amplitude of the frequencies 6-10 cps in the depth leads. More quantitative data on spectral densities become available when further analyses have been completed.

However, it is possible at this stage to state unequivocally that the EEG records have revealed clearly, changes associated with extreme alerting and with impaired cardiovasuclar reflex control. In the latter phase, the records indicated strong probability that there were epochs of impaired attention likely to be associated with defective judgement.

Plate 3 also shows an open circuit noise test of the entire system. This test was conducted immediately after the cables were removed from the animal and all other connections were still intact.

Although definitive conclusions are impossible on the basis of the results of one experiment, certain impressions seem sufficiently clear to merit further investigation. Also, some improvements in methodology suggested themselves as indispensable in future experiments. Several of these are summarized as follows:

<u>Follow up experiments</u>

1. The relationship of CNS activity to cardiac anomalies.
2. The separation of visual and proprioceptive input, especially during the spin phase.
3. Investigation of a larger number of areas in the brain, especially as regards bilateral symmetry.

<u>Modifications in methodology</u>

1. Increase the number of available EEG channels.
2. Provide better synchronization between the experiment and the recording.
3. Attempts to improve EKG electrode system.

In spite of the need for additional experiments incorporating these improvements it was clearly shown that an animal implanted in this way, together with the instrumentations used, yield significant physiological data scarcely obtainable in any other way.

Monkey Centrifuge - Spin Run   N6 Dec. 1963.

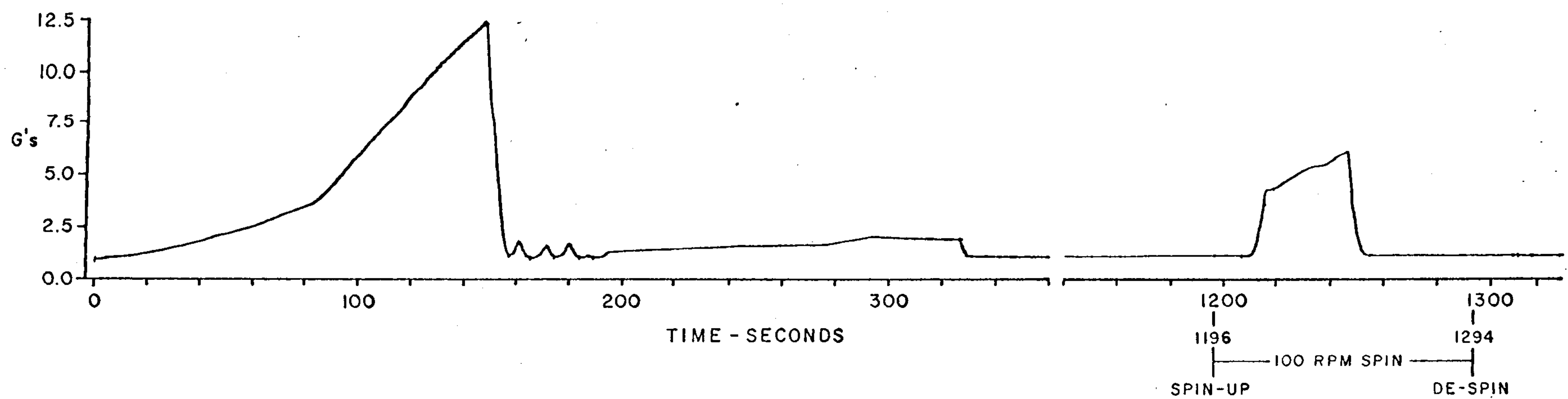
12-11-63   EEG Running Commentary. Time - 5 sec/page.

Pre run	P. 137	Raised
	160	Turned horizontal. Lying on left side.
	182	Lowered into position (face down)
	194	6/sec high amplitude burst.
First Stage	230	Go. Camera starts.
	239	2 G. Looking around.
	244	3 G.
	248	4 G. Facial distortion.
	251	6 G. Arrhythmia, bradycardia.
	252	7 G.
	253	8 G. Dropping beats.
	254	9 G. Desynchronized.
	256	10 G.
	257	Facial distortion.
	258	11 G. Tongue out. Eyes shut. Tongue and lips discoloring.
	259	12 G. Eyes shut.
	260	Centrifuge down.
Second Stage	262	1 G. Arrhythmia
	263	Desynchronized EEG and slow waves.
	264	Tachycardia but altered complex.
	268	Slow waves gone.
	283-4	Short arrhythmic episode.
	298	Centrifuge stopped.

12-11-63, Monkey Centrifuge, EEG Running commentary cont.

	P. 299	General 3 - 4 cps.
	306-8	Cardiovascular irregularities and high slow waves.
	316	Cardiovascular irregularities and high slow waves.
	322	Eyelids closed.
Coast	398	Camera on.
	440	et. seq. Heart regular.
	450	Start flywheel. Blinking and missed beats.
	460	Eyes partially open.
Spin up	468	Start spin.
	469	Spin and centrifuge to 4 G.
	470-2	Big waves in visual (photic ?)
Third Stage	475	5 G.
	479	6 G.
	480	Centrifuge slowing, still spinning.
Spin down	484	Altered EKG. Amplitude decreased.
	488	Head twitches and tilts 45° to left.
	489	Stop spin.
In orbit	494	Door open.
	504	Turns ~~and~~ to finger~~s~~ snap.
	507	Flipped to horizontal.
	509	Flipped to vertical.
	510	Eyes swollen closed, nose bleeding. EEG resembles control.
	518	Light response. Refuses food.
	534	Shivering.

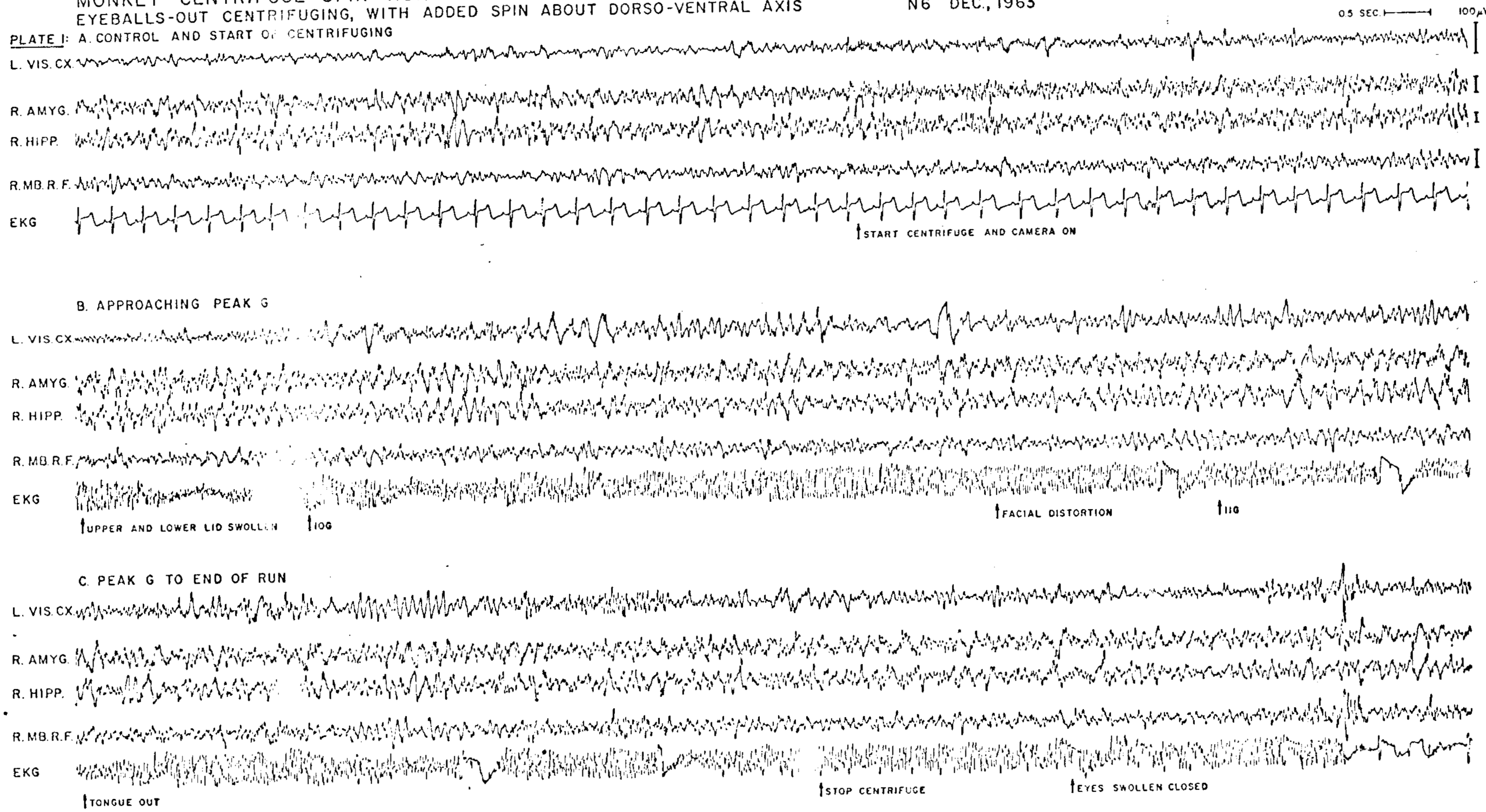
MONKEY CENTRIFUGE-SPIN RUN N6 12/11/63
ACTUAL CENTRIFUGE "G" PROFILE



MONKEY CENTRIFUGE-SPIN RUN

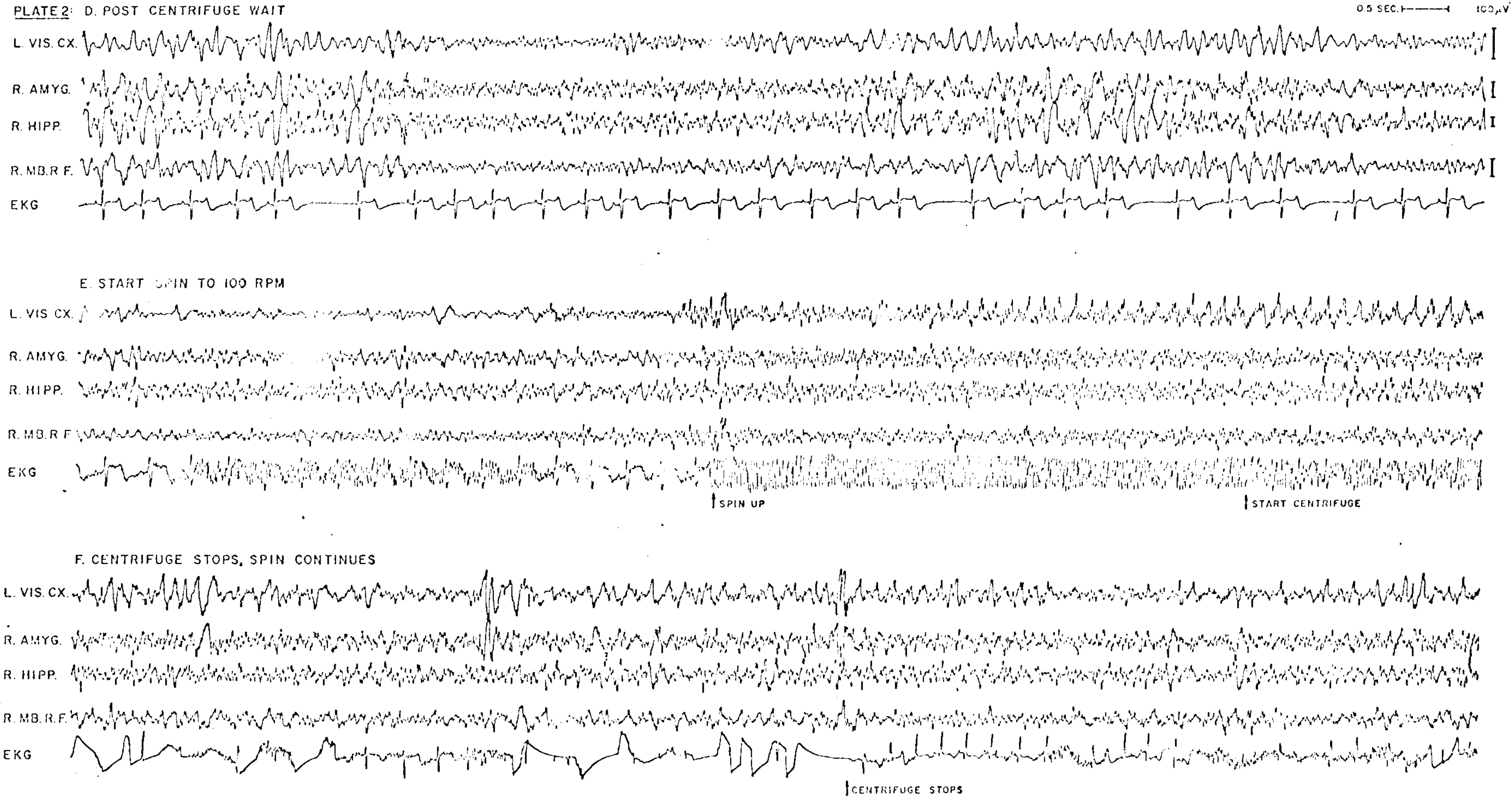
EYEBALLS-OUT CENTRIFUGING, WITH ADDED SPIN ABOUT DORSO-VENTRAL AXIS

N6 DEC., 1963



MONKEY CENTRIFUGE-SPIN RUN

EYEBALLS-OUT CENTRIFUGING, WITH ADDED SPIN ABOUT DORSO-VENTRAL AXIS   N6 DEC., 1963



MONKEY CENTRIF[illegible] [illegible]-SPIN RUN

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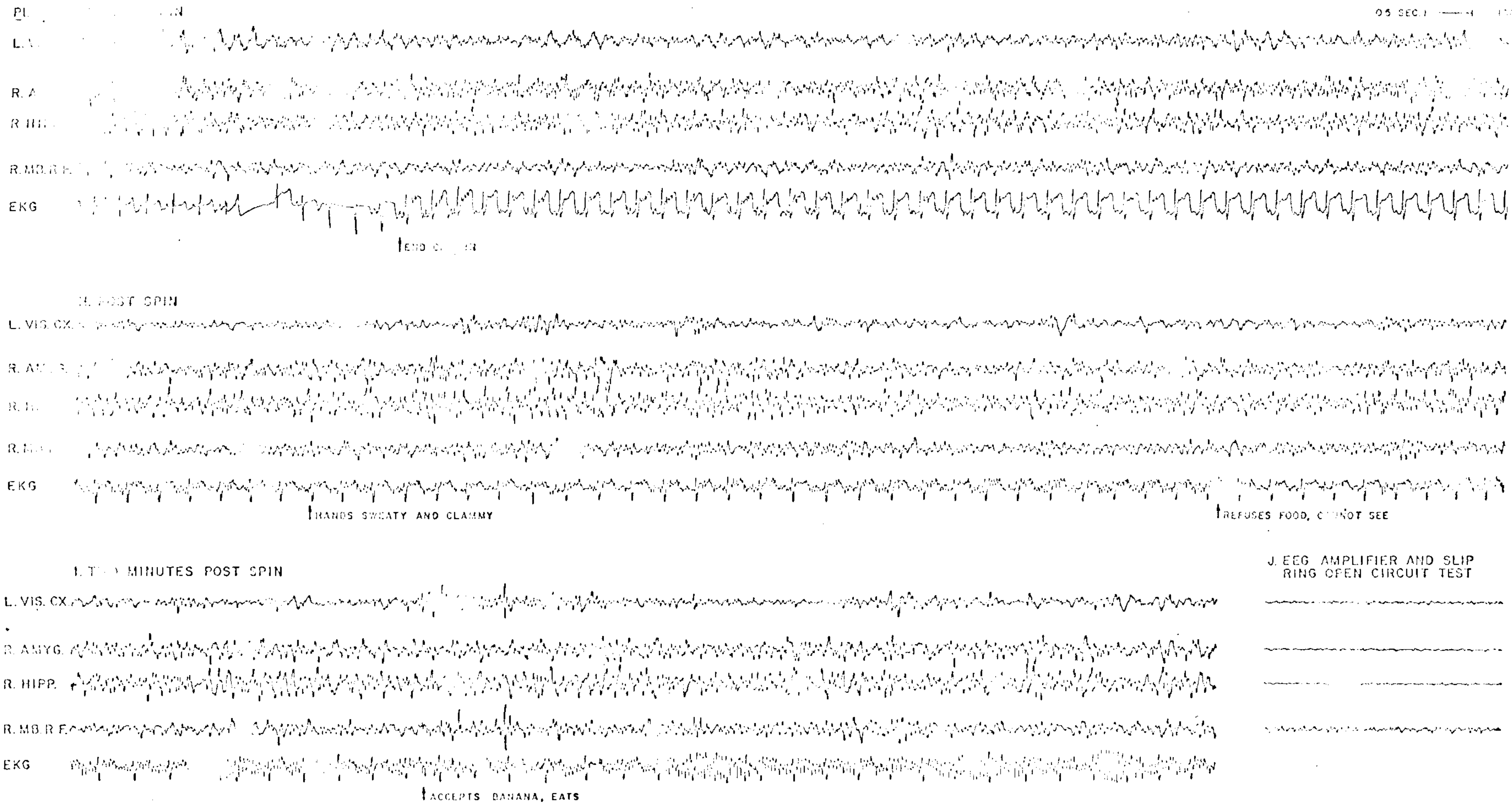

AXIAL ACCELERATIONS OF BIOSATELLITE SPACECRAFT