with slow-wave cycles. All 18 of those occurring within 90 minutes of the onset of sleep were associated with slow-wave cycles, but under normal conditions slow-wave sleep always occurs in the first third of sleep. More crucial to the relation of the release of HGH to slow-wave sleep are the 19 later peaks, recorded during that part of the night when slow-wave cycles are uncommon and stages 3 and 4 occupy only 5 percent of total sleep time. Fourteen of these peaks occurred in slow-wave cycles.

For seven subjects mean values of HGH per sample could be calculated for both slow-wave and non-slow-wave cycles in late sleep. All seven subjects had higher values during slow-wave cycles than during the non-slow-wave ones. Mean value per sample across subjects for these late-night, slow-wave cycles was 3.28 ng/ml, and for the non-slow-wave cycles, 0.65 ng/ml ($P < .02$).

Although the total amount of slow-wave sleep was similar for all subjects, its distribution over sleep cycles throughout the night was variable. Those subjects with more frequent slow-wave cycles had initial peaks of greater magnitude and more frequent secondary rises.

For five subjects sleep-waking cycles were reversed after one or two base line sessions by keeping them awake for 24 hours (Fig. 2). Four were reversed from night sleep to day sleep and one from day sleep, to which he had been accustomed for 2 weeks, to night sleep. None of the five secreted HGH during the wakefulness period corresponding in clock time to the previous 2 nights of base line sleep. Each then secreted HGH during sleep after reversal and during his next reversed sleep period. The basic pattern of release after reversal was similar to that subject's pattern in base line sleep and continued to show a relation to slow-wave sleep (Fig. 2). Three subjects who were reversed from night to day sleep had peaks of greater magnitude during their first sleep period after reversal.

Data on release of HGH during sleep in previous studies (*1–3*) and the data presented here favor the existence of a neural control mechanism of growth hormone releasing factor from the hypothalamus in addition to those mechanisms already studied (*9*).

We conclude from our data that this release is related not only to sleep but particularly to non-REM portions of the recurrent cycles within sleep, especially if these include EEG stages 3 or 4. The synchronization of release and sleep patterns implies that related or identical subcortical pathways from brainstem to cortex and hypothalamus are operative.

The reversal of sleep-waking cycles demonstrates further that the rhythmicity of HGH release in sleep over repeated base line records is not due to an inherent circadian rhythm as recently postulated (*9*) but is dependent on the rhythmic recurrence of sleep itself.

Release of HGH in sleep suggests an anabolic function of slow-wave sleep and provides impetus for further study of neuroendocrine rhythmicity in sleep.

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Surveyor Alpha-Scattering Data: Consistency with Lunar Origin of Eucrites and Howardites

The alpha-scattering experiments carried out by Surveyor missions 5, 6, and 7 (*1*) supplied chemical analyses that are not inconsistent with the hypothesis that the eucrite and howardite achondrite meteorites originated on the moon (*2*). Briefly, this hypothesis maintains that the uplands consist of coarse-grained mafic to ultramafic igneous rocks which crystallized at depth, were then fragmented, and were repeatedly mixed to form polymict breccias, of which howardites are samples. The maria are considered younger basaltic rocks of distinctive iron-rich composition, from which eucrites have been derived. Rocks of the uplands are thought to have crystallized early in lunar history, perhaps 4.5×10^9 years ago, and have not undergone significant chemical alteration since then. Age determinations by potassium-argon dating suggest that eucrites are younger, with an average age of about 3.7×10^9 years (*3*). The hypothesis requires that a mechanism, such as meteorite or comet impact, is capable of removing material from the lunar surface, in order that samples can arrive at the earth.

Surveyor 5 and 6 supplied analyses of samples in Mare Tranquillitatis and Sinus Medii, two widely spaced locations covered by dark, flat, typical mare material. The similarity of these analyses to those of typical eucrites (Table 1) has been pointed out by O'Keefe *et al.* (*4*). Surveyor 7 made three similar analyses of a rock and soil in the vicinity of the young upland crater Tycho, apparently on ejecta from the

Table 1. Comparison of composition of eucrites with results of Surveyor 5 and 6 analyses.

Element	Surveyor 5 (atom %)	Surveyor 6 (atom %)	Juvinas eucrite (atom %)*
C	< 3	< 2	
O	58 ± 5	57 ± 5	60.6
Na	< 2	< 2	0.3
Mg	3 ± 3	3 ± 3	3.8
Al	6.5 ± 2	6.5 ± 2	5.6
Si	18.5 ± 3	22 ± 4	18.7
"Ca"	13 ± 3	6 ± 2	4.6
"Fe"		5 ± 2	6.2

* Composition of Juvinas eucrite (percent by weight) and range of eucrites (in parentheses): SiO_2, 49.32 (48.6–49.6); TiO_2, 0.68 (0.4–1.0); Al_2O_3, 12.64 (11.7–13.9); FeO, 18.49 (15.3–20.1); MgO, 6.83 (5.4–7.4); CaO, 10.32 (8.6–11.5); Na_2O, 0.42 (0.4–0.9); K_2O, 0.05 (0.04–0.22); Cr_2O_3, 0.30 (0.06–0.9); MnO, 0.53 (0.3–0.8); P_2O_5, 0.09 (0.09–0.16); FeS, 0.53 (0.03–0.57). See (*2*).

Table 2. Composition of howardites and a hypothetical plagioclase-pyroxene rock as compared to Surveyor 7 analysis.

Mineral	Atom percentage of							Percentage (by weight) of						
	Si	Al	"Fe"	Mg	"Ca"	Na	O	SiO_2	Al_2O_3	FeO	MgO	CaO	Na_2O	Cr_2O_3
Howardites	18–18.6	2.3–5.0	5.8–6.8	4.6–11.5	1.7–3.7	0.1–0.6	60.0–60.4	48.6–49.5	5.1–11.1	16.0–20.4	8.1–20.5	4.0–9.0	0.2–0.8	0.4–1.3
Hypothetical plagioclase-pyroxene* rock	17.7	8.9	2.4	4.8	4.7	0.4	61.0	49.0	21.0	8.1	8.9	12.3	0.6	
Surveyor 7 samples	18 ± 4	9 ± 3	2 ± 1	4 ± 3	6 ± 2	< 3	58 ± 5							

* Sixty percent plagioclase, $An_{90}Ab_{10}$; 40 percent pyroxene, $En_{62}Fs_{31}Wo_7$.

crater (*5*). These data are not directly relatable to the chemical composition of howardites, but the following considerations suggest that the Surveyor 7 analysis is consistent with that of plagioclase-rich rocks that occur as fragments in howardites.

Chemical analyses of howardites and eucrites can be recalculated to mixtures of three components, An (anorthite, $CaAl_2Si_2O_8$), En (enstatite, $MgSiO_3$), and Fs (ferrosilite, $FeSiO_3$), which represent the major mineralogical constituents of these meteorites—calcic plagioclase feldspar and calcium-poor pyroxene. A triangular plot of these components is a convenient way to compare the major compositional features of the meteorites and the Surveyor analyses (Fig. 1).

If the Surveyor 7 analyses were reduced to a consideration of these components, the results would correspond to a rock with about 60 percent feldspar (by weight) and 40 percent pyroxene (by weight), an unusual type of terrestrial or meteoritic rock. Table 2 shows the comparison of data from Surveyor 7 with that for a mixture of plagioclase and pyroxene (60:40) in which the plagioclase ($Ab_{10}An_{90}$) and pyroxene ($En_{62}Fs_{31}Wo_7$) compositions are similar to those observed in the meteorites and include the most important of the minor constituents omitted in the diagram (Ab, $NaAlSi_3O_8$, and Wo, $CaSiO_3$). The comparison shows that, within the uncertainties of the Surveyor 7 data, the analyzed rock may consist of minerals identical to those of howardites. However, if the Surveyor data are assumed to be valid, the proportions of calculated feldspar and pyroxene are dissimilar to those of most howardites.

Howardites and the rock analyzed by Surveyor 7 cannot be compared directly, because the howardites are thorough mixtures of a wide variety of mineral and rock fragments; Surveyor 7 analyzed a single rock fragment and nearby soil of similar composition. If the fragment analyzed is a primary rock, and not merely consolidated soil, the similarity between rock and soil analyses suggests that mixing of a variety of rock types has not been extensive. Howardites, which do not contain rock fragments as large as that analyzed by Surveyor 7, have been homogenized considerably. (The range of bulk compositions of howardites is much smaller than the range of mineral compositions.)

Fragmentation and mixing of howardites preclude the determination of the ratios of feldspar to pyroxene in the original rocks, but the existence of feldspar-rich and pyroxene-rich rocks in the original rock assemblage can be inferred (*2*). Coarse pyroxene fragments and the pyroxene-rich bulk composition of several howardites indicate that coarse-grained, pyroxene-rich rocks have existed; the hypersthene achondrites, which may be related to eucrites and howardites (*6*), are essentially pyroxene rocks composed of one mineral. The Serra de Magé meteorite, generally called a eucrite, is a coarse-grained, nonbrecciated meteorite consisting of about 80 percent plagioclase. The existence of this meteorite and the Moore County meteorite, which is slightly enriched in plagioclase, demonstrates that feldspar-rich rocks are components of the eucrite-howardite sequence. The feldspar enrichment of Serra de Magé defines a range of feldspar-to-pyroxene ratios that includes the Surveyor 7 analyses.

These results indicate that, within the limits of the presently stated analytical errors, the Surveyor 7 analyses are included by the range of compositions of howardites and related meteorites. In that rock assemblage, such plagioclase-rich rocks are rare and are believed to represent crystal accumulates formed under slow crystallization of ultramafic magma (*2*). With refinements of the Surveyor data, it may be possible to decide between the eucrite-howardite hypothesis and other suggestions for the composition of lunar surface rocks, such as the tholeiite–high aluminum oxide basalt hypothesis presented by Jackson and Wilshire (*7*). The sodium content of eucrites and howardites would rarely be greater than 0.8 atom percent, whereas the typical terrestrial volcanic rocks generally contain 1.5 to 3.5 percent sodium.

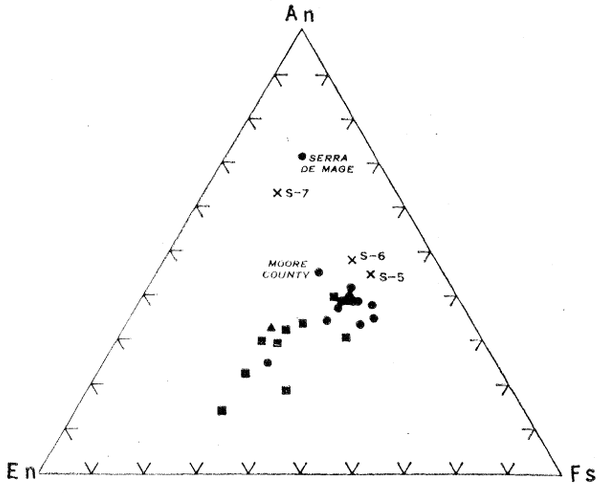

Fig. 1. Triangular plot of major components of eucrites and howardites compared with results of Surveyor analyses. Circles represent eucrites; squares indicate howardites, as defined by Duke and Silver (*2*). Two eucrites, those from Serra de Magé and Moore County, are enriched in feldspar with respect to all other eucrites and howardites. The triangle represents a mesosiderite, with a silicate composition similar to that of howardite.

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Cyclamates and Human Cells

Stone *et al.* (*1*), reporting on cytogenetic effects of cyclamates on human cells in vitro, state that a concentration in vitro of 200 μg of cyclamate per milliliter is equivalent to a dosage of 15 g per 75 kg of body weight. This dosage is simply equivalent to a concentration of 15 g per 75 kg of culture medium. There is an implication here, possibly not intended by Stone *et al.*, that a blood concentration of 200 μg of free cyclamate per milliliter can be obtained by an oral dose of 15 g to a man weighing 75 kg. This is manifestly not the case. The absorption of orally administered cyclamate is variable, but is considerably less than 100 percent and, of the amount absorbed, only about 40 percent is free, the remainder being bound to plasma proteins. Also, absorbed cyclamate is rapidly excreted in the urine, so that it is impossible to maintain any particular concentration in the blood for any length of time with a single oral dose. If the cyclamate were ingested over the period of a day, the peak concentrations in the plasma would be lower, with a higher dose being required to achieve a given concentration in the plasma.

In one study by Wiegand, single oral doses of 5 g of sodium cyclamate given to two human subjects resulted in peak concentrations in the plasma of 21.0 and 17.8 μg/ml. This suggests that a dose of about 50 g would be needed to obtain a plasma concentration of 200 μg/ml and that, to obtain such a concentration of free cyclamate, a dose of 125 g would be required, 35 times the daily maximum of 3.5 g suggested by the Food and Drug Administration.

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Goodhart has correctly pointed out that we did not intend to suggest equivalence between the dosages employed in vitro and blood concentrations of free cyclamate in vivo. What we did point out was that in an average man (75 kg) the dosage in vitro would be equivalent to 15 g of the compound in his body. The problems of absorption, protein binding, and excretion are, therefore, pertinent when comparisons with human intake are to be made, and these have been properly brought up by Goodhart. (i) Actually we have no information on protein-binding of cyclamate in the in vitro systems employed nor whether such binding confers biological activities. With regard to the data offered by Goodhart, information available to us on cyclamate balance studies during daily ingestion in the human is sketchy and variable, with average recoveries, in some instances, being as low as 30 percent. If the low concentrations in the plasma (and interstitial spaces) quoted by Goodhart (Wiegand's data) apply to the low excreters, then cyclamate concentrations in the cells may be relatively high, or possibly even concentrated in specific tissues or cells, such as the bladder and gastrointestinal tract.

Further work may clarify some of the points raised by Goodhart. Our group now has evidence that rats raised on small quantities of cyclamate (substantially less than a daily ingestion of 3 g per 75 kg of body weight) exhibit differences in maze performance as compared to control animals.

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Procarbazine: Chemical Immunosuppressant Also Powerful Carcinogen

Stewart and Cohen (*1*) report that procarbazine is an effective immunosuppressant. The implication was that procarbazine might be preferred to antilymphocytic serum.

Procarbazine (MIH) is a valuable drug in cancer chemotherapy, particularly in certain often fatal conditions such as Hodgkin's disease, malignant melanoma, and bronchogenic carcinoma. Sartorelli and Creasey (*2*) have reviewed biochemical and pharmacological properties of MIH which bear on the varied biologic and pathologic effects of this compound.

However, it is also important to realize that this compound, and indeed analogous structures, are powerful carcinogenic and teratogenic agents (*3*). The carcinogenicity appears specifically related to the presence of the benzylmethylhydrazine side chain, also present in the carcinogens azomethane, azoethane, and 1,2-dimethylhydrazine (*4*). This class of compounds, which, like dialkylnitrosamines, are metabolized to active carbonium ions (*5*), is among the most dangerous of carcinogens known. Considering the high degree of carcinogenicity of procarbazine, its practical application as an immunosuppressant would seem unwise where extended survival is expected.

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