

Chapter 9

Digestion and Absorption

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Rapid, ongoing advances in spaceflight technology constantly pose new challenges for space biology and medicine. For example, attention devoted during the early stages of space exploration to the technological challenge of providing foods for consumption in space has been supplanted to some extent by renewed interest in the physiological aspects of nutrition and digestion in microgravity. Indeed, as the duration of flights continues to increase, the importance of space nutrition and digestive functions also increases, to the point where these issues may actually limit the safe duration of space explorations.

The digestive tract is highly sensitive to environmental factors as well as changes in the body's own *milieu intérieur*. Modern gastroenterology has provided a wealth of information concerning the fundamental principles underlying digestive-system function, especially on the transformation of complex nutritional substances into forms that can be absorbed readily for further metabolism. Food is hydrolyzed largely in the stomach and the small intestine, the latter through the actions of pancreatic enzymes and bile. Hydrolysis and absorption are facilitated by gastrointestinal (GI) motility. Membrane digestion, discovered in the late 1950s, plays an important role in absorbing nutrients.¹ Digestion is ultimately regulated by neural and hormonal mechanisms, and thus GI function can be affected indirectly as well as directly. The response of the digestive system to spaceflight and other extreme conditions illustrates this point.

The history of space gastroenterology can be traced from an early report published in 1965,² which was considered of interest mostly to aviation medicine, to a Russian monograph published in 1981³ describing studies of digestive-system function in cosmonauts during short- and long-term flights, to a more recent book on digestion during hypokinesia.⁴ This chapter describes current findings on gastroenterology in space, and includes results from studies of the human digestive system conducted aboard spacecraft, during acceleration tests, and during hypokinesia (head-down tilt bed rest). We propose that understanding the mechanisms of digestive-system functions during spaceflight will allow us to predict which disorders could arise during flight and to take steps to prevent and treat them. This information could also facilitate the discovery of ways to increase human tolerance to the spaceflight environment and thus enhance human performance in

that unusual environment. Finally, such information would provide a physiological rationale for nutritional recommendations for both the in-flight and postflight periods.

I. Spaceflight and the Human Digestive System

Early in-flight data on the human digestive system were quite limited, consisting entirely of anecdotal reports from crew members.^{5,6} No GI tract changes were noted by astronauts after the Mercury and Gemini missions.⁷ However, the incidence of clinically significant GI symptoms increased with increasing flight duration. A decreased sensation of thirst has been reported by crew members during flight regardless of their actual hydration status, perhaps due to reductions in blood renin concentrations. Appetite reportedly was reduced at times, as was taste sensitivity and the taste appeal of some food products.⁸ Other symptoms described have included increased flatulence in the stomach and intestines, the sense of the stomach being displaced toward the diaphragm, and constipation, particularly during longer flights. Nausea and vomiting during the first hours and days of flight are common, and may reflect disturbances in the vestibular system as the crew members begin adapting to weightlessness.³

The first formal study of human digestive-system function in space took place on Soyuz-9.³ Since that time, 45 cosmonauts from short-term flights have been studied and 30 from long-term flights (including the Salyut-4, Salyut-6, Salyut-7, and Mir missions). Preflight-to-postflight comparisons were supplemented with in-flight GI studies beginning with the Salyut-7 missions.

GI function has been studied by following the appearance of digestive enzymes in the blood (incretion) and their elimination from the body (excretion) in urine and feces; these measures are believed to reflect the state of the digestive glands that produce the enzymes.^{3,9} Another method, developed jointly by Russian and French investigators, involved assessing gastric acidity with an "Acidotest," and assessing the blood-glucose response to carbohydrate loading by using a glucometer and "Dextrosticks."¹⁰ A more comprehensive assessment of GI morphology and function was developed and implemented during the fourth and fifth Mir missions. This assessment involves glucose-lactose loading and subsequent analysis of the glycemic response; measuring gastric acid pro-

duction; and obtaining ultrasound scans of the liver, gall bladder, pancreas, and major blood vessels of the abdominal region.¹¹

A. Preflight-to-Postflight Comparisons

1. Short-Term Flights

GI tract enzymes. A group of 45 cosmonauts studied before and after 7- to 8-day flights all showed a tendency for blood pepsinogen to be greater after landing than before launch, suggesting that the chief cells within the gastric glands had been activated; pepsin concentration in urine, however, was virtually unchanged from before to after flight. Blood gastrin concentrations also tended to be greater after flight than before.

Preflight-to-postflight changes in blood concentrations of the pancreatic protease trypsin were inconsistent. Similarly, amylase excretion was unchanged, but pancreatic amylase concentrations in blood, and in some cases in urine, seemed to be higher after flight. Pancreatic lipase activity in blood remained within normal limits for most crew members, but some 20% of the group studied showed postflight increases in pancreatic lipase activity in blood, but not in urine.

No changes were noted in the amounts of intestinal enzymes in feces after short-term flights. Monoglyceride lipase and alkaline phosphatase activities were similar to preflight measurements. Postflight saccharidase activity was negatively correlated with preflight activity, i.e., those with high preflight activity had low activity after landing, and those with low preflight activity had high postflight activity. At the same time, dipeptidases, especially those for glycyphenylalanine and glycylnorvaline, were increased after landing relative to before flight.

These results suggest that weightlessness may enhance hydrolysis of nutrients in the GI tract, especially the first and last phases of protein hydrolysis. The observed tendency for increases in primary and membrane-protein hydrolysis probably reflects a nonspecific stress response.^{12,13}

The most important factor in adapting to extreme environments is the body's ability to make uninterrupted use of energy-rich nutrients for biosynthesis.¹⁴ The digestive system is a component of a larger functional system that regulates nutrient levels in the body.¹⁵ The biosynthesis process increases the demand for amino acids, which precipitates increased utilization of free amino acids in plasma.¹⁶ The combination of observed increases in protein aggregation in the GI tract with a tendency for activation of the carbohydrase enzyme chain (which supplements the supply of high-energy glucose substrate) tends to support the notion that early exposure to weightlessness is associated with a new level of metabolic-process regulation.

Gastric motility and emptying. Gastric motility was assessed in 20 cosmonauts before and after flight by means of electrogastrography.¹⁷ The mean number of stomach contractions per minute before flight was three; the amplitudes were normally distributed, with a mean of 0.10 ± 0.16 mV (range =

0.30 mV). After a 2-day flight on Soyuz-12, the mean amplitude of stomach contractions decreased, the distribution curve was skewed to the left, and the range was somewhat decreased, although the rate of contractions remained stable. After a 7-day flight on Soyuz-13, mean amplitude of stomach contractions remained depressed for 4 days. Also, the mean peristaltic wave frequency in the stomach was the same as the preflight baseline, but its rhythm was irregular, ranging from 2.8 to 3.2 contractions per minute. Gastric emptying was increased after flight relative to before.

2. Long-Term Flights

We assessed GI function in cosmonauts before and after flights lasting from 30 days to 1 year; because of the limited number of subjects, data points were combined for statistical analyses. The results of our analyses are presented below.

GI tract enzymes. Plasma pepsinogen results are illustrated in Fig. 1. In general, plasma pepsinogen was elevated during the first few days after flight, but had returned to preflight baseline levels by 10 days after landing. However, pepsinogen remained above preflight level 10 days after a 326-day flight (1.4 x baseline), but was reduced (also by a factor of 1.4) during the first 5 days after a 366-day flight.

The amounts of trypsin, amylase, and lipase in blood before and after flight are depicted in Fig. 2. Trypsin concentration was nearly always elevated after flight relative to before, with the elevation tending to return toward preflight baselines as time went on. However, blood trypsin concentrations *increased* during the recovery period after some of the longer flights. For example, blood trypsin was depressed the first 10 days after 237- to 241-day flights, but increased later, reaching a mean of 11.3 ± 1.4 mmol/L compared to the baseline of 3.3 ± 0.9 mmol/L. Changes in blood amylase concentration, by contrast, were more consistent after the longer flights, with early preflight elevations decreasing toward baseline with increasing recovery time (Fig. 2). Blood lipase concentrations varied widely after landing (Fig. 2).

Preflight and postflight comparisons of pepsinogen, amylase, and lipase in the urine are shown in Fig. 3. Urinary pepsinogen concentration tended to be greater after landing than before flight (preflight mean 0.037 ± 0.002 g/h·L), except for measurements taken after the 366-day flight. Amylase excretion was largely unchanged except for after the 326- and 366-day flights, when they peaked to 9.99 ± 1.6 and 23.5 ± 3.8 kg/h·L, respectively. The presence of lipase in urine after flight was more variable.

Changes in amounts of fecal enzymes are illustrated in Fig. 4. Fecal dipeptidase exceeded 5 mmol/g on the first to fifth days after 96- to 125-day flights; after 175- to 185-day flights, this elevation remained through 10 days after landing. On the other hand, mean fecal dipeptidase was only 0.68 ± 0.26 mmol/g for up to five days after 237- to 241-day flights. Fecal saccharidases (maltase and alkaline phosphatase) were largely unchanged after long flights, but tended to become depressed relative to preflight measures as the recovery pe-

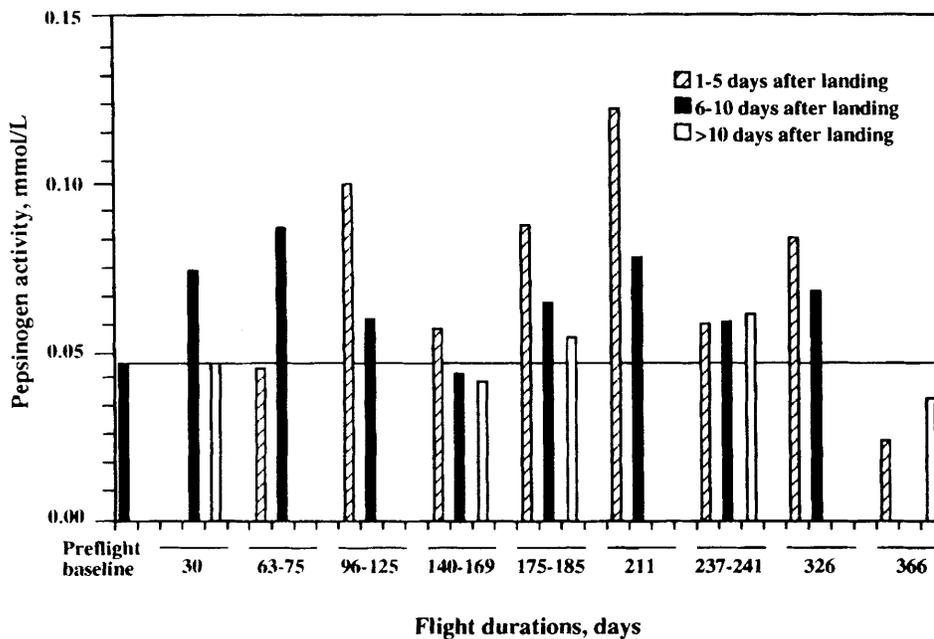


Fig. 1 Blood pepsinogen activity in cosmonauts after spaceflights of various durations.

riod progressed. Fecal monoglyceride lipase levels increased drastically more than 10 days after 140- to 169-day flights, and 6–10 days after a 211-day flight, but otherwise were unchanged from preflight levels.

In sum, changes in the digestive system associated with long spaceflights involve an increase in the peptic potential of the stomach and in pancreatic hyperenzymemia. The severity of these changes may vary as a function of flight duration, onboard conditions, compliance with countermeasures against deconditioning, and the efficacy of these countermeasures. The fitness of individual crew members was negatively correlated with severity of digestive changes. The postflight changes noted in pancreatic enzymes may indicate diminishment in the hydrolytic potential of that gland in space.

Gastric motility and emptying. Gastric motility in two cosmonauts after an 18-day and a 30-day mission revealed changes in both the amplitude and the rhythm of gastric contractions. On the second day after landing, both subjects on the 18-day Soyuz-9 mission showed increased contraction amplitude relative to before flight, and decreases to 2.5 and 2.4 contractions per minute.³ Subsequent measurements were the reverse of these findings, i.e., contraction amplitude decreased and frequency increased. Amplitude-structure analyses revealed increases in the range of distribution of the absolute amplitude values. This finding was thought to result from isolated high-amplitude contractions that made the curve sinusoidal on the right side. However, most contractions remained in the area of low amplitudes. Gastric contractions were arrhythmic, especially 2–4 days after landing. Changes in amplitude and rhythm of stomach contractions were still present 12 days after the 30-day flight.

Both amplitude and rhythm of gastric contractions were disturbed 8 days after a 63-day flight, with doubled ampli-

tude, much arrhythmia, and significant broadening of the range of absolute values of the amplitude. Curves were sinusoidal at this time. By the 16th day after landing, asynchronies were noted between the body and the pyloric region of the stomach. Gastric motility was decreased after a 175-day flight; changes in contraction rhythm and amplitude were accompanied by a shift of the amplitude distribution curve toward the lower amplitudes. Finally, mathematical analyses verified that gastric emptying was diminished after flight.

B. In-Flight Studies

The first direct studies of the human digestive system during flight took place on the Salyut-7 and Mir-4 missions. Gastric acidity was studied in flight in 10 cosmonauts; the glycemic response to glucose loading was assessed in 12 cosmonauts; ultrasound scans were obtained of the abdominal organs in six cosmonauts; and four cosmonauts were tested during flight with a more extensive battery of GI tests as described below.

Gastric acidity, measured using the "Acidotest," was largely unchanged during the first 60 days in space. By day 120, acidity had declined to the lower boundary of the normal range; at 165 days, acidity had increased greatly. On day 224 of a 237-day flight, all three cosmonauts displayed gastric hyperacidity, which was confirmed by postflight increases in blood gastrin.^{3,18}

When results from the glucose-tolerance test were analyzed with respect to when during the flight the test had been administered, an overall pattern of change was noted in the glycemic curves. A test on flight day 48 revealed blood glucose to be low both before and after the sugar load. This pattern persisted for the first two months of flight. By flight

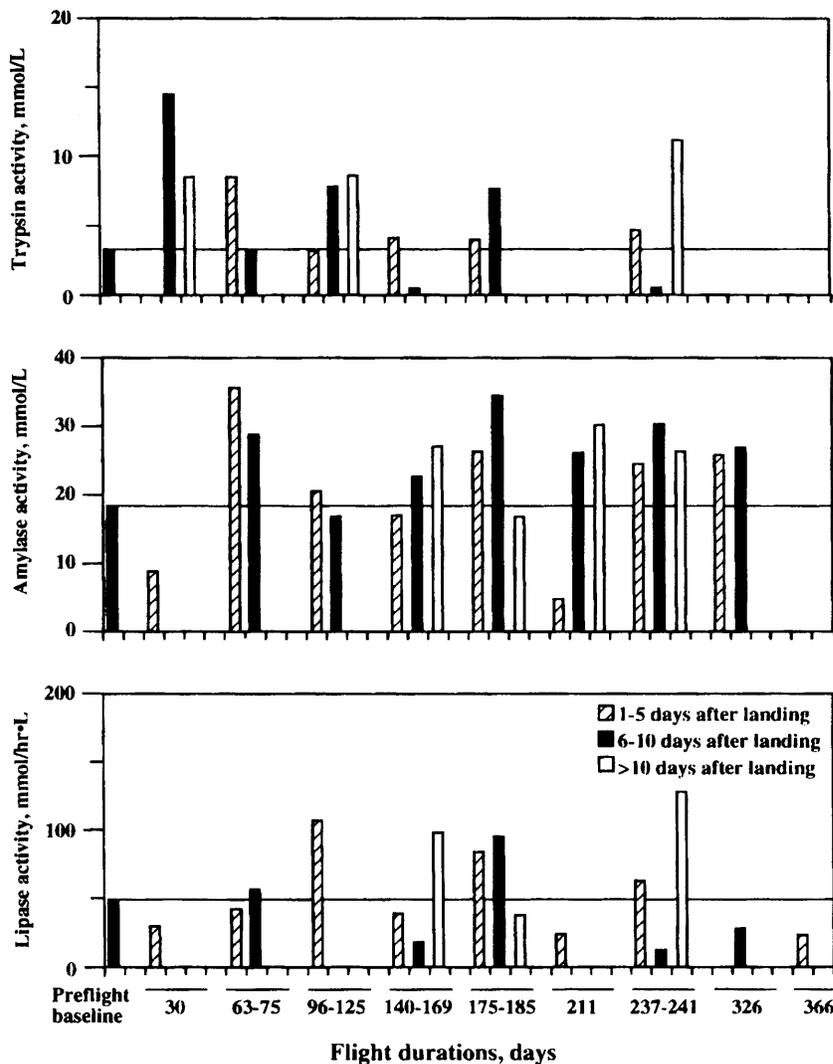


Fig. 2 Blood pancreatic-enzyme activity in cosmonauts after spaceflights of various durations.

days 88–97, blood glucose levels were closer to normal both before and after load, and had increased as expected after the load in two subjects. On flight day 120, the height of the glycaemic curve had increased sharply, and glucose utilization was delayed after sugar loading. Still later in flight (days 158–224), these delays were more pronounced, suggesting a decrease in glucose utilization by tissues. After the one-year flight, blood glucose concentrations after sugar load were greater than preflight values (Fig. 5).

These progressive changes in glycaemic response with increasing flight duration suggested the need for ultrasound studies of the pancreas, liver, spleen, gall bladder, and vessels in the abdominal cavity. During the 237-day flight and the subsequent postflight period, ultrasonography revealed pancreatic edema, deformation of the gall bladder, and atony of the biliary ducts. Beginning on day 21, the first cosmonaut tested displayed a consistent increase in the front-to-back dimension of the liver that persisted until the end of the flight. The second cosmonaut displayed an increase in liver size beginning on day 108 that lasted until the end of the flight. On

the first day after landing, 4 of the 10 cosmonauts tested were judged to have enlarged livers.¹⁹

The fourth and fifth prime crews on the Mir station underwent tests of gastric acidity, gastric emptying, glucose-lactose loading, and ultrasound measurements. On day 189 of the fourth prime crew's mission, gastric emptying was found to be slowed and the liver and pancreas increased in size, the liver by about 1.5 cm and the pancreatic head by about 0.44 cm. These increases were accompanied by a decrease in the exogenous density of the parenchyme of these organs, an ultrasound indicator suggesting edema.¹¹ Bile emptying after glucose-lactose loads in flight was delayed and the glycaemic curves depressed, indicating a general hyperkinesia in the gastrointestinal tract. After landing, one cosmonaut had normal gastric acidity and other had hyperacidity; the visceral organs of both continued to show signs of venous hyperperfusion. The hyperglycaemic curves were higher after flight than during, probably from delayed utilization of blood glucose, but bile evacuation was enhanced, suggesting hypermotility and emptying of the gallbladder.

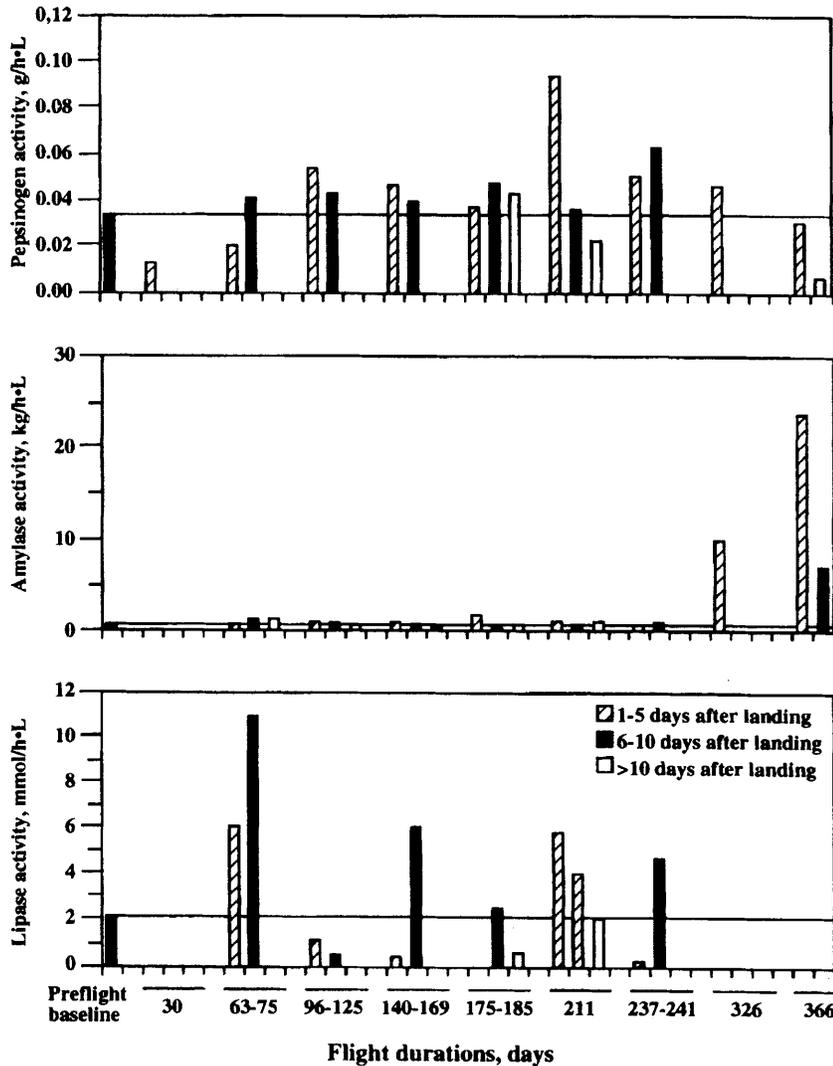


Fig. 3 Digestive enzymes in cosmonaut urine after spaceflights of various durations.

Members of the fifth Mir prime crew also displayed enlargement of the liver and pancreas, depressed ultrasound echoes from the body and tail of the pancreas, and signs of venous engorgement in the organs of the abdominal cavity. One cosmonaut had distended hepatic and splenic veins and pancreatic edema. One subject showed accelerated bile evacuation from the gallbladder followed by rapid filling, while another displayed slowed evacuation of bile from the gallbladder with signs of hypertony of the biliary tract. Recovery of blood-glucose level after sugar load for the latter crew member was delayed; the former had a hyperglycemic reaction 30 minutes after the load, which was followed by rapid normalization. The "Acidotest" results suggested gastric hyperacidity in both crew members. Ultrasound tests of these crew members showed some residual symptoms in the viscera two weeks after landing.

These data led us to conclude that the most labile component of the human digestive system on long missions (lasting up to one year) is the gastropancreatic complex. Blood pepsinogen values after flight were not always associated with

flight duration; however, postflight elevations of this compound in urine imply activation of the chief cells of the gastric glands. The postflight finding of increased blood gastrin, taken in combination with several observations of hyperacidity, suggests that long-term spaceflight is associated with gastric hypersecretion.

Depression of gastric emptying accompanied by gastric hypersecretion triggers a sequence of changes in the hepatopancreatic complex. Hyperenzymemia can be associated with changes in microcirculation in the pancreas.³ Elevated enzymes in the blood result in deficits in the pancreatic enzymes required to synthesize proteins, fats, and carbohydrates. This state is accompanied by decreases in the hydrolytic potential of the small intestine, particularly with regard to proteins.

Thus, prolonged exposure to space creates a well-defined state of the gastrointestinal tract, characterized by gastric hypersecretion; decrease in the hydrolytic potential of the pancreas; insufficiency of the endocrine function of the pancreas; "maldigestion"; depression of motility and evacuation functions; venous engorgement in the abdominal cavity; enlarge-

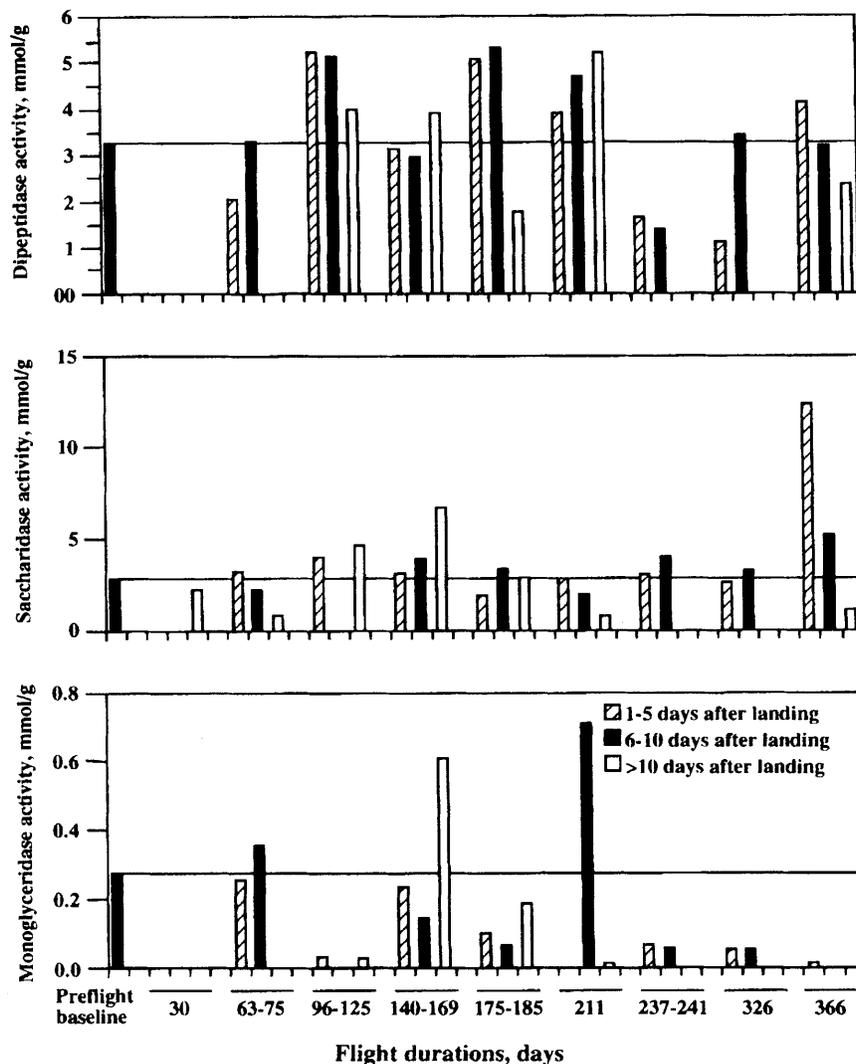


Fig. 4 Digestive enzymes in cosmonaut feces after spaceflights of various durations.

ment of the liver; atony of the biliary tract; and decreased contractility of the gallbladder.

II. Spaceflight and the Animal Digestive System

Animal studies are invaluable in space biology and medicine as a way of elucidating subtleties in the mechanisms regulating the function of various physiological systems. Morphologic changes in the GI system and changes in the activities of a broad spectrum of digestive enzymes were first assessed in Wistar-SPR rats that were flown for 7 to 19.5 days on the Kosmos biosatellites. These studies significantly expanded existing ideas about enzyme secretion and activity in blood and urine during spaceflight. In addition, it was hoped that the results from these studies would enhance understanding of the course of metabolic processes in the body, since the GI tract is both an organ system that hydrolyzes, absorbs, and transports nutrients and an active agent of metabolism that enables chemical processes in the body.

Several groups of rats were studied in order to provide appropriate controls: a spaceflight group, a synchronous ground-control group, and a vivarium-control group. An additional group of rats on the Kosmos-936 mission was exposed to artificial gravity via an on-board centrifuge; this mission included a corresponding centrifuged ground-control group as well. The test (flight) rats were killed either at the landing site within 5–11 hours after landing or on the 25th day after landing. The stomach, liver, pancreas, and small intestine were examined morphologically and histochemically, and the activities of pepsin (a gastric protease), trypsin (a pancreatic protease), amylase (a pancreatic carbohydrase), pancreatic lipase, intestinal carbohydrase-saccharidase, intestinal dipeptidase, intestinal monoglyceride lipase, and intestinal alkaline phosphatase were measured in homogenates of GI organs. The enzymatic activity of the small intestine was compared in homogenized and intact intestinal mucosa, thus allowing the supply of enzyme in the enterocytes to be differentiated from the digestive activity of the intact mucosal sur-

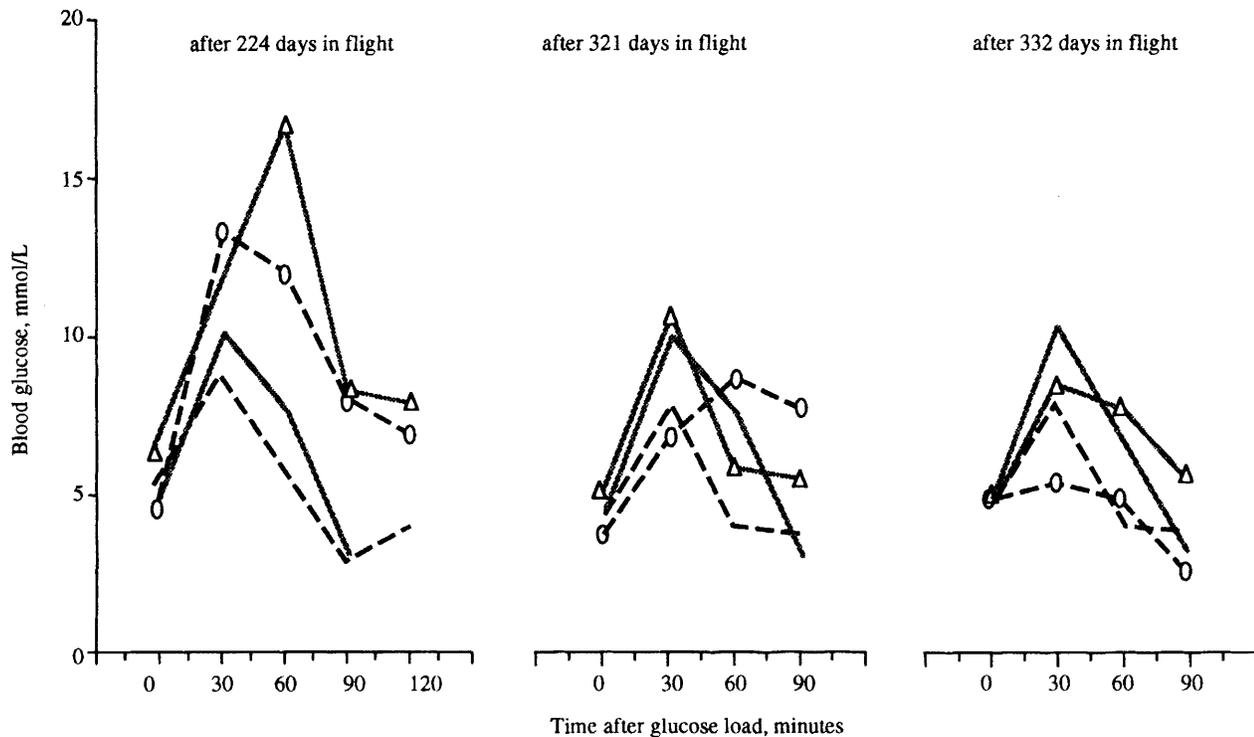


Fig. 5. The effect of 224-day, 321-day, and 332-day spaceflights on the human response to carbohydrate loading. Each pair of lines denotes one subject; lines without symbols are preflight responses, and lines with symbols denote in-flight responses by the same subject.

face. This plan would also allow an indirect assessment of the translocation of the synthesized enzymes and their uptake into the lipoprotein membrane.³ The results from these studies are described in the following paragraphs.

A. GI Tract Enzymes

Pepsin activity in the gastric mucosa was found to increase after both the seven-day Kosmos-1667 mission and after the synchronous ground-control treatment; however, the more pronounced change in the flight group confirms our hypothesis as to the development of gastric hypersecretion in microgravity. These groups also showed drastic reductions in salivary and pancreatic amylase activity, with the reductions being greater in the flight group.³

The distribution of pancreatic amylase in the intestinal mucosa shifted such that the distal end had more enzyme than the proximal end; the activity of γ -amylase, a brush-border carbohydrase, was significantly reduced in the flight group throughout the small intestine. The activities of invertase and maltase, other brush-border enzymes, were no different after treatment than before.

Lipase activity in homogenized stomach, pancreas, and salivary glands after the Kosmos-936 flight is illustrated in Fig. 6. Pancreatic lipase activity was greater in the flight and synchronous control groups after treatment than before, but to a greater extent in the ground-control groups. Pancreatic lipase was consistently redistributed from the proximal to the

distal end of the small intestine, as was pancreatic amylase. The activity of monoglyceride lipase, which hydrolyzes lipids at the brush border, was no different after treatment than before. Amounts of alkaline phosphatase were unchanged in the proximal section of the intestine but were consistently increased in the distal section after flight or the synchronous treatment. These data indicate a slight activation of the lipolytic enzyme system, which was more pronounced in the flight group.

The amount of trypsinogen in homogenized tissue was significantly reduced after flight, but was greater after the synchronous ground treatment than before. At the same time, the activity of dipeptidases (enzymes that hydrolyze proteins at the intestinal brush border) tended to increase throughout the intestine. Statistically significant increases were found for glycyl-L-leucine-dipeptidase in the proximal section of the intestine, and for glycyl-L-methionine dipeptidase. In contrast, the synchronous control group showed decreased dipeptidase activities throughout the intestine.

Longer flights produced the following pattern. No significant changes in pepsin activity were noted in gastric-mucosa homogenates after treatment (flight or synchronous control), whether measured hours or days afterward. The activity of pancreatic proteolases was greatly increased a few hours after treatment (more so for the flight group than for the synchronous control group), but by the 25th day after landing, amounts of trypsinogen and trypsin in pancreatic homogenates from both groups were equal to those of the vivarium control.

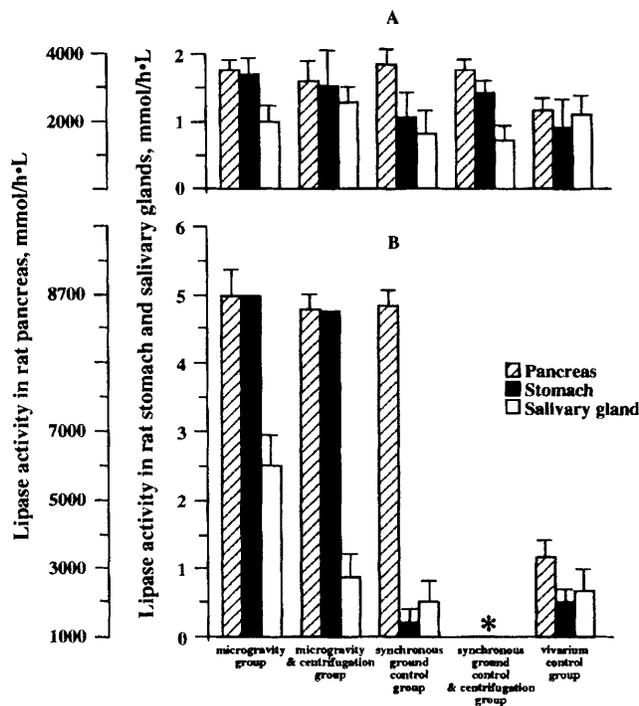


Fig. 6 Lipase activity in pancreas, stomach, and salivary glands of rats flown on Kosmos-936. Top panel, 6 hours after landing, bottom panel, 25 days after landing, *, not studied.

Additional changes in the activity of glycyl-L-leucine-dipeptidase in the small intestine had normalized by the 25th day after landing.

Amylase activity in pancreatic homogenates decreased sharply after flight and the synchronous treatment, but more significantly in the flight group. Saccharidase activity after flight increased in both the homogenate and the surface of the intact mucosa, to the greatest extent in the distal section of the small intestine. By the 25th day after landing, saccharidase activity had decreased, to a greater extent in the homogenate. Saccharidase activity was no different in the synchronous-treatment and vivarium-control groups. Pancreatic lipase activity, and the distribution of this enzyme in the intestinal mucosa, after long flights was similar to that described above for the shorter missions. These results have been confirmed by other investigators as well.²⁰⁻²³

Interestingly, the use of artificial gravity on one of the biosatellites had a positive effect only on proteolytic enzymes (e.g., trypsin and dipeptidase). In all other instances, this treatment either had no effect or intensified decreases in activity (e.g., in pancreatic amylase, intestinal lipase, and invertase.)

To summarize the GI enzyme studies, all animals displayed postflight increases in proteolytic activity, suggesting that the synthesis of these enzymes had been stimulated. These results agree with those from morphological studies of the stomach (see below), and, when taken with the observed increases in blood gastrin levels in humans,^{3,18} further verify a postflight tendency to gastric hypersecretion.

Decreased carbohydrase activity probably makes supplying the body with energy more difficult. Logically, then, fat could become the most important energy source. Postflight activation of pancreatic lipase and decreases in lipolytic activity at the proximal small intestine imply an enhanced release of pancreatic lipase into the blood, as demonstrated by increased lipolytic activity in the stomach and salivary glands.

B. GI Tract Morphology

U.S. studies of the potential for gastric-ulcer formation in rats flown on Kosmos-782²⁴ revealed neither macroscopic nor microscopic evidence of ulcers or mucosal erosion in any animal. After more prolonged flights, however, the surface epithelium of the gastric mucosa had thickened, and the amount of neutral mucopolysaccharides was substantially reduced. Both the flight rats and the synchronous-control group showed cytoplasmic vacuolization and chromatin-poor nuclei in the parietal cells; the activities of succinate dehydrogenase and NAD-diaphorase also was depressed in these cells after flight.^{25,26} These changes are analogous to those occurring in response to stressors, e.g., the administration of glucocorticoid hormones.⁷

The secretion of hydrochloric acid was examined further by assessing the activity of mitochondrial enzymes and ATPase in the secretory membranes of the gastric mucosa (i.e., the parietal cells).²⁷ Electron microscopy revealed changes that were most significant in the flight group (Table 1). Although the mitochondria did not swell appreciably, the area they occupied in the cells increased, probably because their number increased. The surface area of the mitochondrial cristae also increased, because of the combined effects of increased numbers and area of mitochondria and increased density of the mitochondrial cristae. By the 25th day after flight, the mitochondrial morphology had returned to baseline, except for the surface area of the mitochondrial cristae, which remained enlarged.

Table 2 presents results from parallel biochemical studies of homogenates from the same gastric-mucosal areas. The flight rats had greater activity of the following enzymes relative to the ground-control groups: succinate dehydrogenase; cytochrome oxidase; NADH-cytochrome oxidase, NADH-cytochrome, c-reductase, and HCO_3^- -Mg-ATPase. However, the activity of Na,K-ATPase was less in the flight group than in the ground controls.²⁷ The results, taken with the electron-microscopic evidence, seem to indicate that spaceflight has an activating effect on hydrochloric-acid secretion.

Livers of the flight animals revealed changes in lipid metabolism, as manifested by the accumulation of lipid globules of various sizes. Electron microscopy revealed the presence of large lipid inclusions in the sinusoids, and lipids filling the hepatocyte cytoplasm.²⁵ These findings, in the presence of maintained ultrastructure, can be considered evidence for fatty infiltration of the liver. However, this fatty infiltration was reversed by 25 days after landing. Interestingly, fatty infiltra-

Table 1 Parietal cell morphology in rats after Kosmos flights (M±m) (Ref. 27)

Group	Cell position in gastric gland	Mitochondrial area, %	Surface area of mitochondrial cristae	Coefficient of fragmentation of mitochondrial cristae	Index of mitochondrial swelling
Flight group A (5-11 hours after landing)	Top	39.66±0.31	3.898±0.056	0.667±0.040	0.948±0.049
	Center	39.57±0.27	3.887±0.061	0.636±0.027	0.996±0.041
	Bottom	35.23±0.37	3.236±0.047	0.637±0.024	0.848±0.039
Flight group B (25 days after landing)	Top	32.73±0.29	3.021±0.033	0.751±0.057	0.937±0.51
	Center	39.81±0.031	3.783±0.050	0.793±0.047	0.990±0.054
	Bottom	29.37±0.29	2.740±0.070	0.937±0.043	0.981±0.47
Synchronous control group (5-11 hours after treatment)	Top	37.05±0.41	3.224±0.027	0.721±0.042	1.051±0.06
	Center	41.93±0.32	2.156±0.024	0.777±0.041	1.015±0.054
	Bottom	28.6±0.38	2.156±0.024	0.777±0.041	1.015±0.054
Vivarium control group (5-11 hours after treatment)	Top	30.85±0.31	2.482±0.097	0.634±0.047	0.912±0.049
	Center	39.44±0.27	3.356±0.063	0.657±0.033	0.989±0.061
	Bottom	28.06±0.32	1.627±0.005	1.135±0.046	0.986±0.053

Table 2 Enzyme activity in the gastric mucosa of rats after Kosmos flights (Ref. 27)

Group	Cytooxidase	Succinate dehydrogenase	NADH-cytochrome oxidase	HCO ₃ ⁻ · Mg ²⁺ -ATPase	Na ⁺ , K ⁺ -ATPase
<i>After 5-11 hours</i>					
Flight	90.2±1.7*	12.8±0.95*	462±24.5	3.2	0.59
Synchronous control	60.8±7.7	10.4±5.2	287±57	2.07	1.9
Vivarium control	67.4±2.3	8.55±0.95	295±21.2	2.3	51.7
<i>After 25 days</i>					
Flight	68.4±3.4*	18.5±1.0	191±9.2	4.6	--
Synchronous control	57.9±3.1*	12.3±2.6*	225±10.8*	3.36	--
Vivarium control	62.7±4.9	22.3±0.95	285±21.5	3.1	--

Units are mM/g protein/min. *Significantly different from vivarium control

tion was less severe in centrifuged flight animals than in noncentrifuged flight animals.

Light and electron microscopy of the pancreas from the flight and synchronous-control groups revealed a characteristic retardation of the accumulation and secretion phases. Large numbers of mature zymogen granules were accumulated in the apical sections of acinar cells, specifically among the cisternae of the endoplasmic reticulum. These findings were not observed in the control groups. Inactive Golgi apparatus were observed, but neither condensation vacuoles nor "open granules." The entire secretory cycle of the pancreatic acinar cells was inhibited to some extent, most significantly in the flight group.²⁶ Other electron-microscopic changes in the flight animals were a disappearance of alpha-cells from the islets of

Langerhans and transformation of exocrine epithelium into endocrine epithelium.²⁸

Electron microscopy of the small intestine from flight animals revealed disruption of the microvilli and fragmentation of the basal cytoplasm of epithelial cells. Individual portions of the microvilli swelled, rounded, and formed vesicles that separated from the parent cell to accumulate between the villi. These enterocytes displayed polymorphous vesicles, large mitochondria with lysed cristae, pronounced broadening of the endoplasmic reticulum, and accumulation of lipid globules.²⁹ Another experiment on Kosmos-1887 involved measuring the mitotic index, villus height, and crypt depth in the proximal, medial, and distal sections of the small intestine. The flight animals were found to have high mitotic indices

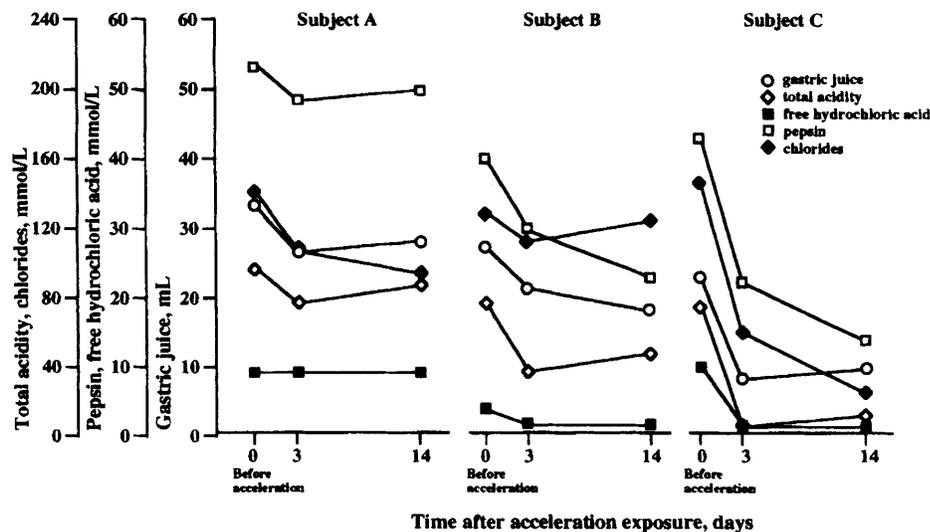


Fig. 7 Effects of acceleration on gastric secretion in three human subjects. Subject A was exposed to acceleration at +10 Gx for 20 s; Subjects B and C were exposed to +4 Gx and +6 Gx for 120 s. Subject B had experienced many previous accelerations; Subjects A and C had not.

upon landing, but the intestinal-cell renewal process had returned to normal in this group.³⁰

III. Acceleration and the Digestive System

Acceleration, one of several factors of the spaceflight environment, is known to have significant effects on the digestive system.³ The following section describes results from acceleration studies with humans, with dogs, and with rats.

A. Human Studies

GI function was assessed in 13 healthy young men after a single exposure to acceleration beginning at +4 Gx for 120 seconds and progressing to +8 Gx for 60 seconds and finally +10 Gx for 20 seconds. All subjects had passed a rigorous medical examination and laboratory tests. Gastric secretory functions also were assessed by using a gastric probe in three subjects once before and then 3 and 14 days after centrifugation (Fig. 7).

Acceleration to +10 Gx for 20 seconds was found to depress the secretion of gastric juices, to the greatest extent in fasting subjects; acid formation, total chlorides, and pepsin secretion were all diminished relative to basal levels. Two men who underwent simulated acceleration on the centrifuge as control subjects also manifested some decreases in the basal amount of gastric secretions on the second day after confinement in the centrifuge chamber.

The activity of pancreatic enzymes and duodenal contents was investigated in two subjects.³ On the second day after centrifugation to +10 Gx for 20 seconds, one subject's amyloid activity had increased by a factor of 4.5 and lipase and trypsin by a factor of two; the other subject had no appre-

ciable change in these enzyme systems over the six days following centrifugation.

Gastric motility studied in three subjects revealed decreases in the force of gastric contractions on the third, seventh, and fourteenth days after centrifugation; these decreases were particularly pronounced on day three. Contraction amplitudes diminished by almost a factor of two compared with baseline measures, and had not reverted to normal by 25 days after centrifugation. Notably, acceleration did not alter the rhythm of peristalsis.

B. Canine Studies

Thirty-eight dogs were exposed to a single +10 Gx acceleration for four minutes on a centrifuge with a radius of 3.7 m. Immediately after centrifugation, all dogs displayed unstable gait, rotating in place, and attempted to lie down. Blood was detected in gastric and intestinal juices and in feces beginning 2 to 3 days after acceleration and persisting for two weeks. Gastric-juice secretion was suppressed by nearly a factor of two for 15 days after acceleration; the time pattern of secretion was distorted as well, with the maximum being displaced by four hours (Fig. 8). Total acidity, total chlorides, and free hydrochloric acid all declined during this period. By 20 days after acceleration, secretory processes became activated: pepsin activity doubled compared to baseline (Fig. 8), and cyclic changes in pancreatic-enzyme activity were observed as well (not shown).

Secretory functions of experimentally isolated small intestine were studied in three dogs with Thiry-Vella fistulas. Amount of intestinal juice increased the first day after acceleration and decreased thereafter, with the decrease lasting for six months. Invertase activity was increased on the day after acceleration, both in homogenate of intestinal juice and in its

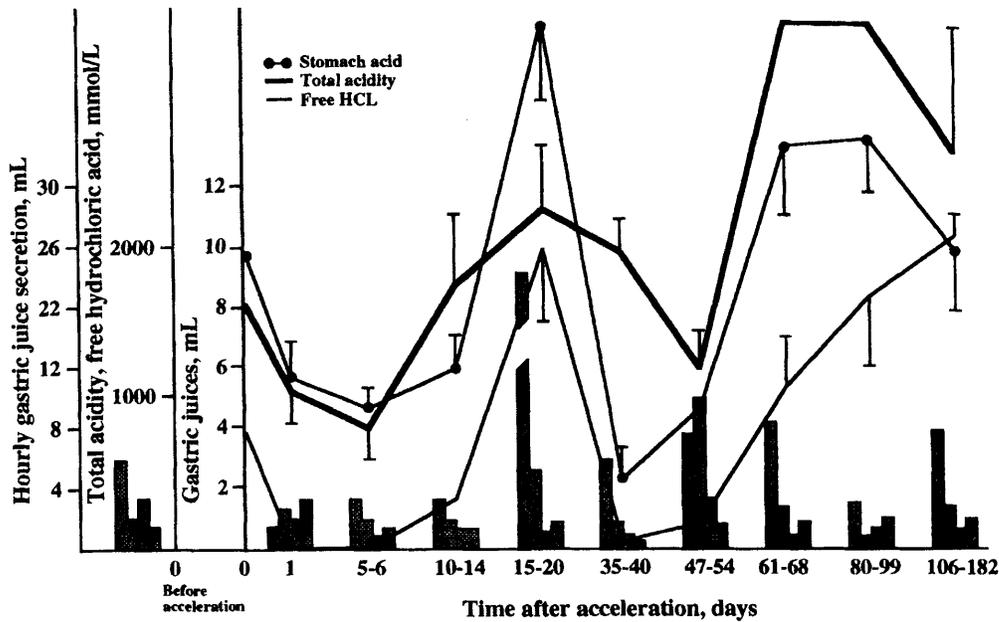


Fig. 8 Effect of +10 Gx acceleration for 4 minutes on gastric secretion in four dogs. Bars illustrate hourly secretion patterns of gastric juice.

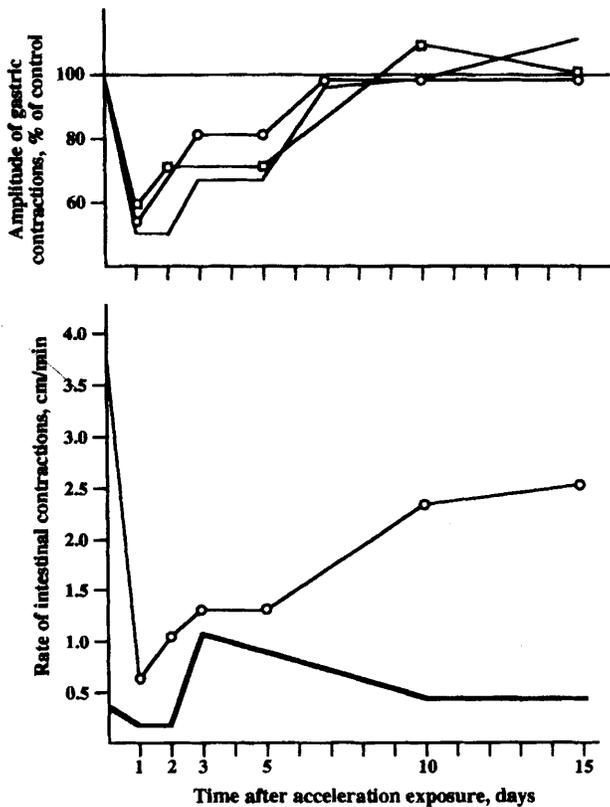


Fig. 9 Effects of +4 Gx acceleration for 4 minutes on gastric contractions and rate of displacement of a free balloon along the intestinal loop in five dogs. Each line represents a single animal.

dense portion. Saccharidase activity was slightly increased over baseline measures, and persisted for five months. Glycyl-leucine dipeptidase activity was somewhat depressed the first few days after acceleration, but on days 2 and 10, dipeptidase activity increased sharply, especially in the dense fraction of the intestinal juice. Alkaline phosphatase activity declined during the first two days after acceleration, after which it increased and subsequently fluctuated. Enteropeptidase activity was depressed starting the first day after exposure and continuing throughout the study. Enzyme activity in fecal extract was similar to the results described above.

Motility of the stomach and small intestine was studied in nine dogs by using balloonography.³ No gastric contractions were present for three hours after acceleration, but motility was present continuously thereafter in fasting dogs. Contraction amplitude was depressed (Fig. 9), but the rhythm remained the same as before acceleration. Periodic activity began to be reestablished by 20 days after acceleration, and was restored completely by days 35-45. Gastric motility during digestion was recovered by day 45. No contractions were present in the small intestine for two hours after acceleration; motility of the upper regions of the small intestine decreased gradually for both propulsive and nonpropulsive motor forces.³

Five of the 22 dogs exposed to +10 Gx acceleration for four minutes died between 40 and 50 days after the acceleration. Postmortem examination of these animals revealed a bluish tinge to the organs of the abdominal cavity, except for the stomach and the upper third of the duodenum. Blood clots were present in the stomach, and the gastric mucosa had thinned and eroded, with ulcerations of various sizes located chiefly in the pyloric area. Many blood clots were found

throughout the small intestine. Liver size was significantly decreased, and hemorrhages were noted in the head of the pancreas.³

C. Rodent Studies

White rats (n=100) were also subjected to one-time exposures to +10 Gx for 20 minutes, on the same centrifuge as that used for the dogs. Three, 6, 24, 48, or 72 hours after acceleration, the rats were killed by decapitation and enzyme activities measured in blood and organ homogenates as described below.³

Pepsin activity in gastric-mucosal homogenates was slightly increased three hours after acceleration, although much variation was present; proteolytic activity in the gastric mucosa was decreased between 6 and 72 hours after acceleration. Plasma pepsinogen was significantly depressed from 3 to 72 hours after acceleration. Amylase activity in both blood and pancreatic homogenates was decreased at three hours after acceleration, but proteolytic activity tended to increase. Amylase and trypsin concentrations in blood gradually returned to normal over the ensuing 72 hours.

Saccharidase activity changed only minimally in the distal region of the small intestine, but increased by 60% in the proximal region. The activity of these enzymes in homogenates of the small intestine had decreased by 40–50% three hours after centrifugation, after which it increased gradually to reach normal levels by 48 hours. Glycyl-leucine dipeptidase activity was elevated at three hours, after which it gradually decreased. After 72 hours, dipeptidase activity was greater than control levels in all regions of the small intestine, as was enzyme activity in homogenized intestinal mucosa.

D. Possible Mechanisms

The direction and magnitude of functional changes in organ systems under exposure to acceleration depends on the peak value of acceleration, jolt, duration of exposure, direction of mechanical forces, number of repeated exposures, and the adaptive potential and initial functional state of the organism. +Gx acceleration is the best tolerated and most thoroughly studied of the acceleration forces; however, it does induce significant changes in the function and morphology of the digestive system.

The magnitude of +Gx acceleration was found to influence the gastric-secretion reaction to that acceleration in studies of dogs with Pavlovian gastric fistulae. Exposure to four minutes of +4 Gx acceleration led to short-term stimulation of gastric secretion, increased pancreatic-enzyme activity, shifts in the enzyme activity of the small intestine, and short-term depression of gastric and intestinal motility. Exposure to +8 Gx for the same time generally produced cyclic changes in the functioning of gastrointestinal organs, although the first day after exposure was marked by depression of secretion and motility functions. Acceleration to +10 Gx, also for 4 minutes, produced long-lasting changes in the digestive system.

Although hour-by-hour secretion of gastric juice was not affected by +4 Gx acceleration, acceleration to +8 or +10 Gx distorted that rhythm by the fourth hour of the experiment, suggesting profound changes.

Another important factor in the development of functional shifts in the digestive system is the duration of acceleration. Long exposures to relatively low acceleration forces can induce profound changes in humans, e.g., gastric-juice secretion, acid formation, and pepsin and mucoprotein production (Fig. 7). Moreover, rats exposed to +10 Gx for 10 minutes showed no evidence of change in active transport of glucose across the intestinal wall or in liver secretory functions, but rats exposed to +5 Gx for 20 minutes did.³ The duration of the recovery period also seems to be proportional to the acceleration magnitude.

Previous exposures to acceleration can also affect the extent of functional change, as illustrated in Fig. 7. Subjects B and C in this study were both exposed to +4–6 Gx for 120 seconds. However, Subject C was being centrifuged for the first time, and Subject B had been exposed to accelerations of various magnitudes and durations for several years. The differences in their results attest to the influence of previous experience on the gastric secretion process.³

The initial state of the individual being exposed also affects that individual's reaction to the exposure. For example, all subjects exposed to +10 Gx for 20 seconds or to +4–6 Gx for 120 seconds showed some inhibition of gastric-juice secretion, acid formation, and gastric-enzyme activity. However, the extent of that inhibition depended on the typical state of the gastric glands for that individual. Accelerating hyperacidic individuals at +4 Gx for 120 seconds reduced their gastric acid to normal levels; however, exposing these individuals to 60 seconds at +8 Gx the next day *increased* their gastric acid. Hypoacidic individuals reacted to acceleration by reaching "normal acidity" (Fig. 10).

The vagus nerve also contributes substantially to GI reactions to acceleration as well as other spaceflight factors. Dogs with stomachs denervated according to Haidenhein's method (local vagotomy) and then subjected to +8 Gx acceleration for 3 minutes failed to show the hypersecretory peaks or spontaneous secretion typical of intact dogs. Gastric secretion was depressed on days 1, 3, and 5, and pepsin activity and chlorides continued to be suppressed for 17 days after acceleration (Fig. 11). Decreases in stomach secretion were noted mainly during the first, complex reflex phase. The concomitant decrease in chloride concentration accompanied by insignificant changes in acidity could be explained by secretion of mucous by the fundus glands.³

Vagally intact dogs exposed to +10 Gx for four minutes showed a sharp increase in amylase and lipase activity but a significant decrease in trypsin during the first few days after exposure. Vagotomized dogs, in contrast, had a smaller increase in amylase activity and a larger increase in trypsin during the same period.

Left cervical vagotomy led to increases in both the liquid and solid components of intestinal juice; subsequent exposure

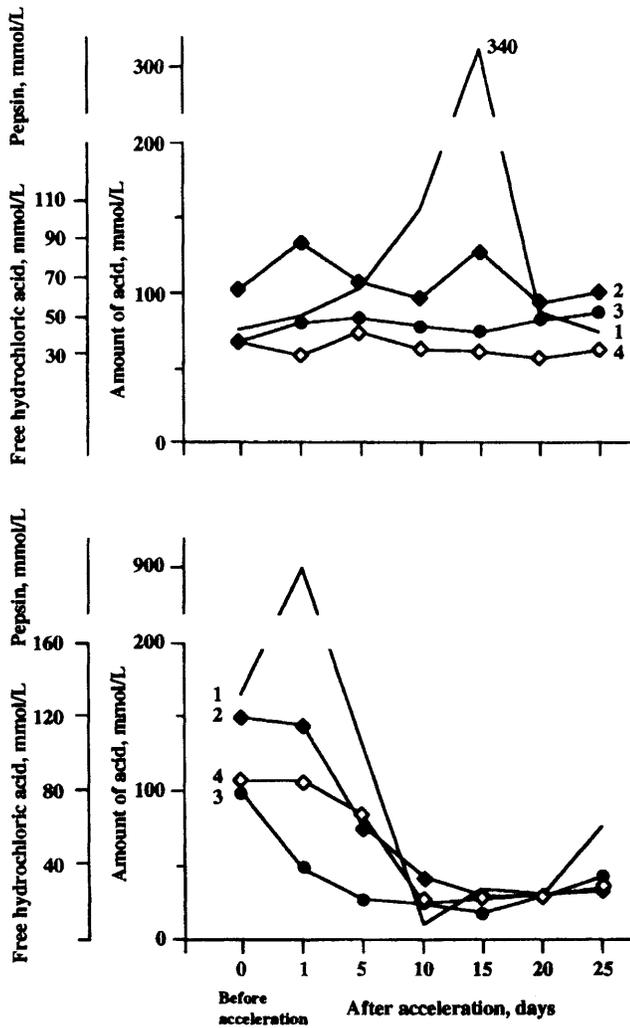


Fig. 10 Effects of +4 Gx and +6 Gx acceleration for 120 seconds on gastric secretion in humans with normal stomach acid (top panel) or hyperacidity (bottom panel). 1, amount of gastric juice; 2, total acidity; 3, free hydrochloric acid; 4, pepsin.

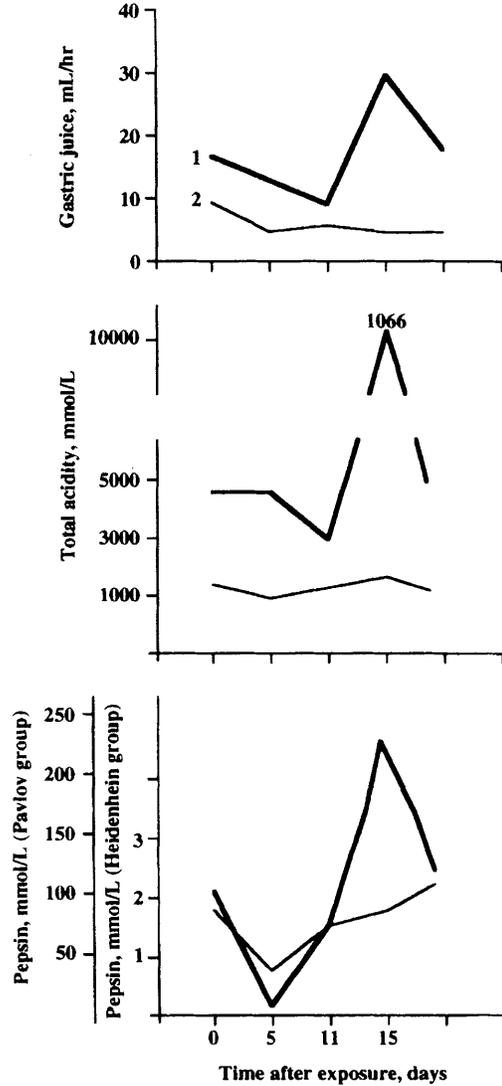


Fig. 11 Effects of +10 Gx acceleration for 4 minutes on gastric secretion in dogs with Pavlovian fistulae (bold lines) or denervated by Heidenheim local vagotomy (light lines).

to +10 Gx acceleration for four minutes increased and then decreased saccharidase activity. Intact animals exposed to acceleration showed a lasting increase in saccharidase activity. Taken together, these results underscore the importance of the central nervous system in the GI reaction to acceleration and other spaceflight phenomena.

IV. Spaceflight Factors and the Digestive System: Hypokinesia

A. Human Studies—Head-Down Bed Rest

The following paragraphs describe two assessments of digestive function during bed rest, the first at -4° head down for 49 days (17 subjects), and the second at -5° head down for 120 days (nine subjects).⁴ Digestive-enzyme activity in these

subjects was studied in the contents of the GI tract as well as in blood, urine, and feces. Gastric-juice acidity was measured through standard titration and intragastric pH measurement.³ Motility and evacuation were assessed by using electrogastrography.¹⁷

The first few days of bed rest brought some complaints of feeling too full after having eaten; by the end of the first week, some subjects noted epigastric discomfort and heaviness, with heartburn and belching appearing shortly thereafter. Although appetite initially increased, it became diminished after a month of head-down bed rest. Other reports included an unpleasantly bitter taste in the mouth, stomach discomfort and rumbling, and flatulence. Palpation revealed transient hypersensitivity about the pyloric region. The liver was enlarged, with its edge 3–4 cm or more below the arc of the ribs. Virtually all subjects were constipated, and some developed hemorrhoids.

1. GI Tract Enzymes

Pepsinogen production was assessed in terms of pepsin activity in gastric juice as well as the amounts of pepsinogen in plasma and urine.⁹ These indicators were measured both in unstimulated and stimulated conditions. In the unstimulated condition, pepsin was reduced relative to control values after 24 days of bed rest; on day 44, absolute values of pepsin returned to baseline, but the gross amount remained significantly diminished, as did secretion of gastric juice. When gastric secretion was stimulated, on the other hand, pepsin activity and gastric-juice production at day 24 increased accordingly, becoming statistically significant on day 44. Plasma pepsinogen was decreased on day 21, but had returned to control values by the end of the bed-rest period. Uropepsinogen concentrations were variable, at times decreased (days 6–8) and at other times elevated (days 10–15). Secretion of this proenzyme eventually returned to control values by the end of the bed-rest period.⁴

Amylase secretion was significantly depressed on days 3, 21, and 48, and amylase and trypsin activities in the duodenal contents were decreased. Trypsin secretion rose to—and sometimes exceeded—control values during the recovery period; a gradual increase in blood trypsin activity continued until the end of the treatment (Fig. 12).

Pancreatic-lipase activity in duodenal contents was drastically reduced during bed rest, ranging from 71% of baseline on day 20 to 50% on day 67 to 5% on day 89 and 11% on day 112. By the 10th recovery day after bed rest, pancreatic-lipase activity was still significantly depressed relative to control values. Renal excretion of lipase remained within normal limits throughout the study.

Changes in blood concentrations of pancreatic enzymes, accompanied by inadequate activity in the small intestine, can indicate pancreatic malfunction. Ultrasound scans of the pancreas in bed-rested subjects confirmed the presence of pancreatic enlargement, particularly of the head, and an increase in acoustic density (a sign of parenchymal edema). These characteristics did tend to return to normal during the recovery period.^{4,31}

Saccharase and maltase activities in duodenal contents were unchanged throughout the hypokinesia period, with the exception of some mild declines in the activities of these enzymes on day 67. Peptide hydrolase activity was progressively depressed throughout the bed-rest period and persisted during the first two weeks of recovery. Intestinal dipeptidase activity in feces was decreased, and returned to normal levels only slowly during the recovery period. Monoglyceride-lipase activity in duodenal contents fluctuated during the bed-rest period, being increased before day 68 and decreasing gradually thereafter.

2. Gastric Acidity

Free hydrochloric acid gradually increased during bed rest; on day 40, its amount in unstimulated secretions had increased

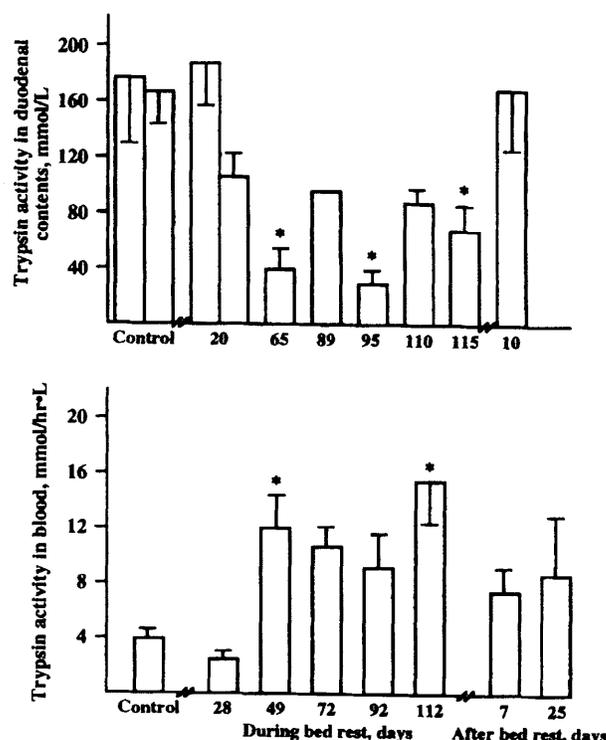


Fig. 12 Trypsin activity in human duodenal contents (top) or blood (bottom) before, during, and after 120 days of head-down bed rest.

to 30 times the baseline, and was double the baseline when stimulated. Figure 13 illustrates the change in gastric pH in subjects during a 120-day bed-rest period. By the end of the baseline period, the pH of basal (unstimulated) secretions had increased in both cardiac and antral regions, and the pH of stimulated secretions increased in the cardiac region.⁴ Regional acidity fluctuated over the course of the bed-rest period. During the first month, the unstimulated pH in the antral region tended toward the alkaline, but stimulated pH was unchanged. Cardiac pH, both on an empty stomach and in response to food, was little different from the first control measurement but less than the second. Individual differences, however, were striking, although all tended to revert to normal values during the recovery period.

Gastrin concentration was only slightly increased during the first 28 days of bed rest, peaked on day 45, and thereafter remained elevated, although variability among individuals had obscured this effect by day 112. Gastrin concentration was still elevated on the 25th recovery day.⁴

3. GI Motility and Emptying

The amplitude of stomach contractions was markedly depressed in all subjects during the first 17 days of a 49-day bed-rest treatment. Motility was reduced by 50% in those who had normal initial motility and by 29% for those who began the treatment with hypokinetic motility. On days 20–35, some

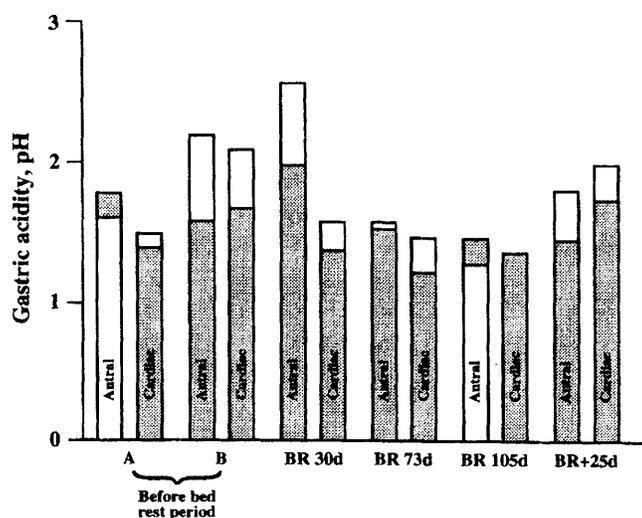


Fig. 13 Regional gastric acidity in humans before, during, and after 120 days of head-down bed rest. Shading in each bar represents pH in the stimulated condition.

moderate stimulation appeared and the range of frequencies broadened. On days 35–49, electrical activity of the stomach again became depressed; motility decreased by 40–50% in those with normal initial motility and by 15% in those with hypomotility. Gastric emptying slowed during this period, with the delay in gastric emptying coinciding with periods of constipation. By the 60th day of recovery, amplitudes were still fluctuating.⁴

4. Glucose Tolerance

The blood-glucose curve that appears after a subject consumes a glucose dose is an important indicator of the hydrolysis, absorption, and utilization of carbohydrates. The ascending portion of these curves reflects the hydrolytic-transport processes in the GI tract, and the descending portion reflects glucose utilization as determined by liver and pancreas function.

Nine subjects underwent glucose-tolerance testing during the 120-day bed-rest study.⁴ In the first of two experiments, two subjects had high baseline blood-glucose concentrations. Blood glucose peaked 30 minutes after sugar load, and returned to baseline concentrations 120 minutes after the load in all subjects. On the 43rd day of bed rest, both basal and stimulated blood-glucose concentrations had diminished, but glycemia still peaked 30 minutes after loading, and sugar utilization was complete in all subjects 120 minutes after dosing. By 75 days of bed rest, the glycemic peak was much higher than baseline as a result of a second glycemic peak 90 minutes after dosing. By the end of the recovery period, basal (unstimulated) blood glucose was the same as the baseline values. The glycemic curve tended to be steeper, with hyperglycemic peaks appearing 30 and 90 minutes after dosing. Most subjects completed the glucose-utilization process by 120 minutes after dosing,

but all aspects of the glycemic curve were significantly elevated.

In the second experiment, blood glucose also peaked after 30 minutes, and glucose had been completely utilized by 120 minutes after dosing. The glycemic curves were flatter and higher on the 43rd day of bed rest, though basal (unstimulated) blood-glucose concentration was unchanged. However, in these subjects, blood glucose peaked at 60 minutes after loading. Blood glucose concentrations had returned to normal after 120 minutes, the coefficient of maximal glycemia was unchanged, and both the intensity of glycemia and the hyperglycemic ceiling increased. On day 82, the glycemic curves were less than baseline, but on day 109 they were higher than baseline, with peaks again at 60 minutes and the curves becoming protracted. The glucose-utilization process had reverted to normal by the 25th day of recovery, although some indicators remained somewhat depressed.

Blood insulin concentrations were elevated by the end of the bed-rest period. One possible explanation for this observation is the tendency in hypokinesia for muscle-degradation products to bind to blood insulin, making the insulin less biologically effective. This supposition is supported by the observed increases in rate of lipolysis and in entry of free fatty acids into the blood.

5. Bile Secretion and Metabolism

Liver excretory function was assessed during the 49-day bed-rest study by measuring duodenal amounts of cholic acid, lipid complex, and total phosphorus. Results were variable, with some subjects showing increases on day 14, decreases on day 36, and increases again on day 49; others showed increases for the first 36 days and decreases thereafter.³ In the 120-day bed-rest study, taurocholic, taurodeoxycholic, glycocholic, glycodeoxycholic, and glycochenodeoxycholic bile acids were studied in duodenal contents. On the 20th day of bed rest, the concentrations of these acids had increased, as had the cholate:cholesterol ratio; both measures declined gradually thereafter. The phospholipid:cholesterol ratio began to increase on day 67 in both bile portions due to increases in phospholipid concentrations in intestinal contents. We conclude from these results that head-down bed rest increases the lithogenic components of bile, thus increasing the risk of gallstones.

B. Animal Studies—Physical Restraint

Groups of 15–20 rats were confined for 7, 30, 60, or 90 days in transparent immobilization cages; their digestive-enzyme activities were measured in blood, urine, and feces as noted above, and measured in gastric-mucosal homogenates as well. Amylase, lipase, and trypsin were measured in pancreatic homogenates as well as in blood. Hepatic production of bile was assessed by inserting a cannula into the bile duct; GI motility was studied through electrogastrography with implanted bipolar electrodes. Gastric and duodenal electrical

activity was recorded before and during the first three hours after feeding.⁴

1. GI Tract Enzymes

Pepsin activity in gastric-mucosal homogenate was significantly increased on the seventh day of restraint, but pepsinogen increment had not changed from control levels. On day 30, pepsinogen was increased, but pepsin activity in the gastric mucosa returned to control levels. On day 60, blood pepsinogen had decreased somewhat, but pepsin activity was unchanged. On day 90, mucosal pepsin and blood pepsinogen were both significantly elevated.⁴ Not surprisingly, blood gastrin levels increased during the restraint period, suggesting that the cholinergic mechanism for increasing the acid-peptic potential of the stomach had been triggered. During the 60-day immobilization, gastric-mucosal glycoproteins decreased; such a change in the mucous barrier would lessen the stomach's protective capacities, and may lead to gastric hypersecretion.

On day seven, amylase activity in pancreatic tissue had more than doubled, but amylase increment was unchanged; pancreatic amylase had returned to normal amounts by day 15. Amylase activity in both pancreas and blood began to decline on day 30. By day 60, and continuing through day 90, blood amylase remained depressed but its activity in tissue increased. Pancreatic trypsinogen was elevated on day 30; blood trypsin was slightly increased as well. Pancreatic trypsin began a gradual decline on day 60, but blood trypsin activity remained at control values.

Restraint for as few as seven days produced significant decreases in pancreatic lipase activity in blood, but not in pancreatic tissue. By 30 days, tissue-lipase activity—but not blood-lipase activity—had decreased significantly. This decline in tissue lipase activity was pronounced from day 60 through the end of the experiment, but its level in blood nearly tripled during this time.

During the first seven days of the experiment, both basal (unstimulated) and stimulated blood insulin concentrations were somewhat diminished. By day 15, both the basal and stimulated levels had increased. On day 90, basal blood insulin was depressed but stimulated insulin was somewhat greater than baseline measures. Blood glucagon concentrations were elevated throughout the 90-day period.

Enzyme activity in the small intestine fluctuated between the 7th and 90th days of restraint. Amylase, saccharidase, and maltase activities were depressed in the proximal and distal regions of the small intestine for the first 60 days, but had increased sharply by day 90 in both sections. Pancreatic (absorbed) lipase activity was elevated for the first 30 days and depressed from day 60 through the end of the experiment. Monoglycerol-lipase activity alternated between periods of depressed activity (days 7–15, 90) and periods of elevated activity (30–60 days). Animals that were restrained with their heads down at up to a 45° angle showed changes in the activity of intestinal enzymes of still greater magnitude.

2. GI Motility

Myoelectric activity of the stomach⁴ before feeding during the baseline period was marked by slow electrical waves (frequency 5.2 ± 0.02 cycles per minute, amplitude 267 ± 0.15 mV). Feeding the animals increased the amplitude of the slow waves by 150%, and increased their frequency by 13%. Slow-wave frequency began to decrease on the fourth day of restraint, and was significantly so by days 15, 60, and 90. The amplitude of the gastric potentials before feeding changed in two phases, beginning to increase on day 4, peaking on day 15, and then declining to the point at which slow-wave amplitudes were 26% less than baseline by day 90. Wave amplitude increased greatly upon feeding the animals, to the greatest extent on day seven (275% of that before feeding). Wave amplitude began to decrease on day 15, and by day 90 equaled 130% of that before feeding.

Myoelectric activity in the duodenum of control animals took the form of slow electrical waves (frequency 39.0 ± 0.76 cycles per minute). The descending segment of the waves revealed a 5.07 ± 0.41 mV spike in a bundle (mean amplitude 732 ± 106.5 mV). Feeding induced a 73% increase in slow-wave amplitude, and frequency decreased by 14%.

Restraint shifted the duodenal slow-wave pattern as follows. On day 45, slow-wave amplitude before feeding began a progressive decline that reached 55% of baseline by day 90. Slow-wave frequency decreased significantly over the same period. Feeding the animals produced the following shifts in wave pattern: The jump in slow-wave amplitude began to decrease on day 4; by days 7 and 90, food produced virtually no response in terms of duodenal slow-wave amplitude. Wave frequency in response to food had decreased by 30% on day 90. The observed decreases in contraction force, frequency, and the myoelectric-activity complex probably explain the relatively slow passage of food through the intestine during restraint.

3. Bile Secretion and Metabolism

Restraining animals for 15 days led to moderate decreases in cholic acid and increases in lipid complex and total phosphorus. On day 30, all three measures were markedly increased, and remained so until the end of the treatment period (120 days). None of these measures returned to normal until 90 days after the end of the treatment period.⁴ Restraining rats in a 20° head-down position for 90 days depressed the rate of bile secretion through day 60; total amounts of bile acids increased gradually, but were depressed on day 90.

The amount of tauroconjugated acids was reduced on day seven; glycodeoxycholic acid, however, was increased. Total acids decreased as a result of a marked drop in taurocholates. Phospholipids declined precipitously (25-fold) on day 30, and cholesterol declined by a factor of two. Total bile acids on day 60 were increased, the glyco:tauro-conjugate ratio was decreased, and the ratios of taurocholic to deoxycholic acids and cholate:cholesterol both increased. By the 90th day of

Table 3 Absorption of ^{131}I -oleic acid and ^{131}I -3,-oleic acid in seven rats during 60 days of horizontal restraint

Substance	Group	Substance Distribution 3 Hours After Administration, %				
		Stomach	Small intestine Proximal	Small intestine Distal	Large intestine	Cadaver
^{131}I -oleic acid	Control	25±0.9	16±2	7±0.5	7±0.8	43±0.9
	Experimental	35±0.8*	14±1.3	7±0.4	6±0.6	35±1.5*
^{131}I -3,-oleic acid	Control	37±2.2	16±3.8	9±2.7	10±1	25±4.4
	Experimental	23±1*	22±2.9	12±2.5	9±0.6	31±3

*Significant differences between control and experimental groups

restraint, the rate of bile secretion had doubled, and the amounts of taurodeoxycholic acid had increased but taurocholic acid and glycoconjugated acids decreased. This change was statistically significant only for taurocholic acid.

4. Glucose Tolerance and Absorption

Carbohydrate absorption and transport was assessed in restrained rats by measuring the transport of glucose across the intestinal wall after an oral dose. The small intestine was obverted and cumulative samples of mucosa prepared so as to allow examination of glucose absorption and transport.³ After only 3 days of restraint, peak blood glucose levels were displaced by 60 minutes relative to controls. On day 7, the glycemic curves were higher and flatter, and on day 15 were lower. This trend began to be reversed after 60 days of restraint. Glucose tended to accumulate in the intestinal mucosa after 15 days of treatment, and the peak accumulation was displaced from the proximal to the distal region of the intestine. These accumulations and displacements increased with time through treatment-day 60.

Lipid absorption was studied after oral doses of compounds labeled with ^{131}I -oleic acid (Table 3). On the seventh day of restraint, the increased rate of absorption of free oleic acid was attributed to a general acceleration in absorption from the small intestine. On day 30, the absorption rate of this compound was unchanged; however, three hours after dosing, evacuation of this compound from the stomach was slowed and its intestinal absorption correspondingly accelerated. Absorption rate of free oleic acid was significantly reduced at this time. Thus, the fatty acids formed from hydrolyzed triglycerides were absorbed quickly, but free ^{131}I -oleic acid was absorbed more slowly. These results are suggestive of a slowing in the absorption of lipid end-products despite the presence of high lipolytic-enzyme activity in the intestine and high concentrations of bile components. On the 60th day of restraint, the rate of absorption of labeled oleic acid was significantly depressed, probably because of its slow evacuation from the stomach, but the rate at which the free form passed from stomach to small intestine was accelerated. On day 90, the

only change noted was slowed rate of absorption of ^{131}I -oleic acid in both the the proximal small intestine and large intestine, despite a compensatory acceleration in absorption in the distal small intestine.

5. GI Tract Morphology

Gastric morphology, histology, and morphometry were analyzed on the 20th day of restraint.^{25,27} Mucus secretion had increased, and parietal cells showed vacuoles forming in the cytoplasm as well as chromatin-poor nuclei. Histoautoradiography revealed decreases in the rate of DNA synthesis. Eosinophils had infiltrated the gastric mucosa. Activity of mitochondrial respiratory-chain enzymes had increased, as had ATPase activity in secretory membranes of chief cells, which confirmed the occurrence of gastric hypersecretion.

Dystrophic and destructive changes were found in the acinal tissues of the pancreas of half of the animals after a 30-day restraint period; vacuolized dystrophy and swelling with cellular disorganization led to destructive changes in acinal tissue, and to destruction of both individual pancreocytes and entire acini.³² Histological examination after 60 days of restraint revealed small loci of chronic inflammation of the interstices and perivascular sclerosis in nearly all of the animals tested. Signs of chronic pancreatitis with symptoms of moderate sclerosis persisted after 120 days of restraint.³²

In another 20-day restraint study, many large and small lipid globules were observed in the liver, mostly toward the centers of the lobes.²⁵ Electron microscopy revealed large lipid inclusions in hepatocytes, the presence of which was attributed to fatty infiltration of the liver. No significant histological changes were found in the intestinal mucosa, submucosa, muscularis, or serosa in these animals. Electron microscopy of enterocytes revealed accumulation of mitochondrial ribosomes and poly-some complexes as well as increased hyaloplasm density. Fragmentation and complete disappearance of microvilli were seen in some cells. Lipids were detected in the enterocytes of villi, in the intercellular spaces, in the basal membrane of the lamina propria between ameboid cells, and in the lymphatic space.

V. Space Gastroenterology: Conclusions and Perspectives

A. Digestive-System Responses to Spaceflight Factors: A Summary

The extent and severity of the changes found to occur in digestive structure and function as a result of exposure to spaceflight and its analogs are directly correlated with the magnitude, duration, and type of exposure to spaceflight factors. These variables affect the rates of hydrolytic and transport processes in the GI tract. For example, for brief exposures to acceleration, the key factor seems to be peak magnitude rather than duration of exposure. By contrast, during longer exposures, the duration of exposure becomes more important than peak magnitude. The digestive-system response may differ as a result of interplay among these factors. Thus, interpreting the shifts observed in secretion and motility must involve consideration of the measured variables with respect to their relation to each other. For example, determining whether flight-related changes in the exocrine apparatus of the pancreas are adaptive or not must involve studying the pancreatic enzymes responsible for hydrolyzing proteins, fats, and carbohydrates. Analytic approaches such as these have allowed us to draw the following conclusions.

Brief exposure to spaceflight factors, mild acceleration, and the early stages of hypokinesia all induce similar, transient reactions in the GI tract. These observations resemble general stress reactions during brief exposures to extreme environments. Longer spaceflights, as well as longer periods of hypokinesia or greater magnitudes or periods of acceleration, tend to induce more specific shifts. The longer recovery times after longer exposures attest to the depth of these changes and the adaptation of the appropriate digestive organs.

The specific changes in the digestive system after long-term spaceflights, or laboratory simulations thereof, are an important part of the human response to microgravity. The results obtained in the studies described herein were closely similar for humans and animals, and are summarized as follows. Gastric hypersecretion develops, with elevated levels of hydrochloric acid in the gastric juice in the interdigestive period and increased proteolytic activity of the digestive apparatus. The exocrine and endocrine functions of the pancreas become insufficient, leading to inadequate amounts of pancreatic enzymes being released into the intestinal cavity but greater amounts being released into the bloodstream (hyperenzymemia). GI motility and evacuation are also depressed in spaceflight. In hypokinesia (bed rest or physical restraint), bile formation and secretion decrease, and lithogenic properties increase. Disorders of protein, fat, and carbohydrate assimilation, associated with changes in hydrolysis and nutrient transport, also have been observed.

In addition to primary effects, GI-tract reactions to spaceflight factors clearly are influenced by secondary effects of the environment as well, e.g., hemodynamic changes and neurohumoral regulation of digestive activity. The conditions of

exposure can be used, to some extent, to predict the depth of the shifts that occur. The initial functional state of an organ and the system to which it belongs have important effects on the nature of digestive-system change. Previous exposures, particularly if habituation is allowed to develop, can play a significant role in predicting responses as well.

B. Fundamental Difficulties and Issues Awaiting Resolution

Several fundamental challenges remain for the field of space gastroenterology. Although the observed results from animal and human studies reported here were similar, extrapolating results from animal studies to humans should always be done with caution. Biological structures and ecological specialization differ between primates, rodents, and carnivores, and should not be overlooked in considering digestive-system tests and their results.

Another traditionally underattended consideration is the period of training and conditioning humans undergo before they are sent into space. Animals, on the other hand, tend to be studied in an unhabituated state so that the effects of acceleration, microgravity, hypokinesia, and so on can be observed in the purest possible form. Repeated exposure to stressors in the spaceflight environment (e.g., crew members who have flown several times) could well lead to attenuation of environmental effects.

The effects of psychological factors on the digestive system also deserve further study. Human awareness of the conditions in which one lives, including the spaceflight environment, is not applicable to animals, which adapt in accordance with laws that we humans still cannot fully appreciate. This standpoint underscores the importance of studying humans in spaceflight, not only from the practical but from the theoretical viewpoint as well.

Findings from human and animal spaceflight studies, as well as experiments to study spaceflight factors on various organ systems, have demonstrated that the digestive system undergoes changes in response to these conditions. These changes logically are compounded by the relatively monotonous space diet. As space missions become longer, the effect of adverse factors on the GI tract, particularly its regulatory systems, will increase. The reactions of the digestive system to spaceflight factors are not yet fully understood, and further investigations are essential.

Future digestive research must include cellular- and subcellular-level studies both in spaceflight and in ground-based simulations. Integrated study of several organ systems, as well as the combined effects of different spaceflight factors, is of paramount importance. Countering impairments in physiological functions and improving crew tolerance of adverse spaceflight factors are other avenues for research, and involve the development of new drugs and other means of protection.

In sum, then, two general directions for strategic research can be defined. The first should be the qualitative and quan-

titative definition of fully adequate secretion, motility and evacuation, digestion, and absorption under conditions in which the body is exposed to factors nonspecific to the GI tract, or a "weak link" exists in the system. Establishment of the latter will allow the field of search to be focused on the appropriate area. These investigations would also involve studying the excretory, detoxification, and immune functions of the GI tract. The next research direction, which initially would overlap with the first, should be to seek palliative and finally preventive measures for those pathologies that are confirmed as being due to spaceflight factors.

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