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Ecological Physiology of Diet and Digestive Systems

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Abstract

The morphological and functional design of gastrointestinal tracts of many vertebrates and invertebrates can be explained largely by the interaction between diet chemical constituents and principles of economic design, both of which are embodied in chemical reactor models of gut function. Natural selection seems to have led to the expression of digestive features that approximately match digestive capacities with dietary loads while exhibiting relatively modest excess. Mechanisms explaining differences in hydrolase activity between populations and species include gene copy number variations and single-nucleotide polymorphisms. In many animals, both transcriptional adjustment and posttranscriptional adjustment mediate phenotypic flexibility in the expression of intestinal hydrolases and transporters in response to dietary signals. Digestive performance of animals depends also on their gastrointestinal microbiome. The microbiome seems to be characterized by large beta diversity among hosts and by a common core metagenome and seems to differ flexibly among animals with different diets.

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INTRODUCTION

Microbiota: all microbes in a well-defined environment

Resource acquisition is a basic task of all animals, and animals have diversified tremendously to make use of the full bounty offered by the Earth's biodiversity. In this review, we discuss digestive features of animals (and their microbiota) that eat a wide variety of food types. Our goal is to present some of the general questions, modes of research, and findings that span and define the field. We build on many fine earlier reviews (1–6). Our focus is on physiological matches with diet among species that might be classified as specialists and thus "major" on certain food types (i.e., the majority of what it eats is a single food type) and those species that are omnivores (eat a variety of foods) or make physiological adjustments as they switch among foods of different composition. Owing to space limitations, we do not review the literature on digestive physiology changes in response to increased/decreased energy demands or to ontogenetic changes in diet. But even after those exclusions, the vast diversity of animals and diets forces our coverage of digestive systems in relation to diets to be extensive rather than intensive, and so we selectively discuss some of the best and/or most recent examples.

We begin with three unifying principles in the ecological physiology of diet and digestive systems. These principles play out in all three major sections that follow: matches achieved between diet and digestion (*a*) in catalytic digesters (animals that rely on endogenous enzymes for digestion), (*b*) in animals that adjust to changes in diet composition, and (*c*) in animals that rely on their microbiota in digestion.

KEY PRINCIPLES IN THE STUDY OF DIETS AND DIGESTIVE SYSTEMS

Variation in Food Chemistry Drives Diversification of Digestive Systems

Features of food chemistry ultimately drive diversification of digestive system morphology, physiology, and biochemistry. There is large variation among foods in both types and amounts of materials refractory (i.e., resistant) to digestion, in the types of main nutritional substrates (e.g., simple and complex carbohydrates, proteins, fats), and in composition within each substrate type (e.g., specific bond linkages, chain length differences) (**Table 1**). Substrate types require different particular complements of secretions and enzymes for their breakdown and particular mechanisms for the absorption of their breakdown products. The time course over which those products are released and absorbed varies widely among food and substrate types. Accordingly, the foods at the top of **Table 1** are composed mainly of sugars, protein, and lipids that can be broken down relatively rapidly by typical enzymatic activities (disaccharidases, amylases, proteases, peptidases, lipases) present endogenously in the digestive tracts of most animals. But as one scans down **Table 1**, the food types have increasing amounts of material, such as plant cell wall or arthropod cuticle/chitin, that is refractory to rapid digestion with endogenous enzymes. At the bottom of **Table 1**, the dry mass of woody vegetation, fungi, and detritus may be composed of 75% or more refractory cell wall material.

Some animals consume foods that contain low amounts of refractory material (e.g., top of **Table 1**), and some of those animals' key digestive adaptations described below are hydrolytic or absorptive capacities that match the relative amounts of carbohydrate, protein, and fat in their diets. But among animals that consume refractory food types near the bottom of **Table 1**, there are multiple strategies. Within many taxonomic groups, there are species that "skim the cream," assimilate cell contents or other nonrefractory materials, and pass the refractory material mainly undigested. Abe & Higashi (7) referred to them as cytoplasm consumers and contrasted them with other species termed cell wall consumers, which extract considerable energy from refractory materials. Among herbivorous mammals, these two extremes are exemplified by, respectively,

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Table 1 Diet items, some of their key chemical components, and enzymes required to break them down[a]

Diet item(s)	Refractory materials or chemical(s)	Less refractory chemical(s)	Enzyme activities[b]										
			1	2	3	4	5	6	7	8	9	10	11
Nectar	Nil	Simple sugars	♦	♦		♦							
Milk	Nil	Lactose	♦	♦				♦					
Animal flesh	Nil	Glycogen	♦	♦	♦	♦							
Insects, zooplankton	Cuticle, chitin	Glycogen, trehalose	♦	♦			♦					♦	
Bacteria	peptidoglycan in G(+) bacterial cell walls	Soluble polysaccharides	♦	♦	♦	♦		♦					♦
Terrestrial plant materials (flowers, seeds, fruits, leaves, twigs)	Celluloses,[c] lignin, insoluble starches[d]	Sucrose, starch	♦	♦	♦	♦		♦	♦	♦			
Aquatic/marine plant materials (green & brown, diatoms, seaweeds)	Celluloses, mannanes, xylans, agarose	Starch, laminarin, and chrysolaminarin[e]	♦	♦	♦	♦		♦	♦	♦	♦		
Plant exudates (saps, resins, latexes, gums)	Phenols and terpene derivatives, hemicellulose, other complex β-linked polysaccharides	Sucrose	♦	♦		♦		♦		♦			
Fungi and lichens	*N*-Acetyl-β-D-glucoaminides, N bound to cell wall components		♦	♦				♦	♦				
Detritus	Celluloses, lignin, xylans, mannanes	Starches, α-glucans	♦	♦	♦	♦		♦	♦	♦	♦		

[a]This table is not comprehensive and lists only the main types of food items discussed in this article. The diet items are ranked (top to bottom) in approximate order of the relative amounts of material in them that is refractory to digestion (low to high). In both vertebrates and invertebrates, digestive efficiency tends to be inversely related to the amount of refractory material in a food (2).

[b]A diamond symbol represents the presence of enzyme activity. Enzyme activities include the following:

(*1*) Proteases and peptidases, which hydrolyze oligopeptides formed by proteases

(*2*) Ester bond hydrolases (e.g., lipase, phospholipase)

(*3–5*) α-Glucosidases: (*3*) α-amylases (hydrolyzes starch from plants and glycogen from animals), (*4*) α-glucosidases [e.g., maltase (hydrolyzes the oligosaccharides formed by amylase), sucrase (hydrolyzes sucrose from plants), oligodisaccharidases], (*5*) trehalase (hydrolyzes trehalose, the principal blood sugar in insects)

(*6–9*) β-Glucosidases: (*6*) lactase, (7) cellulase (cellulose is hydrolyzed by the concerted action of three types of cellulases: endocellulases, exocellulases, and β-glucosidases), (*8*) xylanase and pectinase, (*9*) laminarinase (exo-1,3,-β-glucanases that hydrolyze the major storage polysaccharides in brown algae, laminarin, and chrysolaminarin)

(*10*) Chitinases

(*11*) Lysozyme [hydrolyzes peptidoglycan in G(+) bacterial cell walls (58)]

[c]Cellulose and hemicellulose.

[d]The crystalline pattern of starch seems to determine its susceptibility to hydrolysis (176).

[e]β-1,3-glucan storage products (laminarin) (52).

giant pandas (*Ailuropoda melanoleuca*), which digest less than 10% of cellulose and hemicellulose in ingested bamboo (8), and gorillas, which can digest 45–70% of cell wall material in their herbivorous diet (9). Among birds, examples of cytoplasm consumers are plant cutters (genus *Phytotoma*) that feed almost exclusively on young leaves (with low cell wall content) (10). In contrast, hoatzins (*Ophistocomus hoazin*) and some species of grouse consume leaves, buds, and tips of woody twigs and may digest considerable cell wall material (11). A continuum of feeders/digesters bounded by these two strategies can be found among invertebrate taxa as well. According to Douglas (12), most foliage- and grass-feeding insects [e.g., the locust *Chortoicetes terminifera* (13) and the grasshopper *Aracris flavolineata* (14)] assimilate the most easily utilized compounds (e.g., sugars, starch, and protein) and void the remainder, including cellulose, in contrast to insect species that feed on wood and that exhibit features that enable them to extract energy from cell wall material [e.g., many termites, some cockroaches, silverfish, and firebrats (12)]. Species of herbivorous land crabs range from digestion of little cell wall material up to digestion of nearly 100% of cell wall material (15). The key digestive adaptations for this range of feeders/digesters include cellulases, either endogenous or produced by microbial symbionts, and adjustments in digestive compartment sizes and transit times of digesta through the tract.

Animals have evolved digestive features that effectively process one or a few of these features of foods and substrates, but not features that can effectively process all of them ("jack of all trades, master of none") (16). For the student of diets and digestion, the results are, at first glance, (*a*) a dizzying array of digestive morphologies, physiologies, and biochemistries among animals and (*b*) a complex set of clearly interacting features within an animal. This situation begs for an integrative, systems approach to relate such features to whole-animal feeding rate and digestive efficiency, which are two parameters of nutritional and ecological importance.

Models Help Reduce the Complexity of the Array of Digestive Systems and Guide Mechanistic, Integrative Research

A solution to this challenge, and a major advance in the past two-and-a-half decades, has been the application of chemical reactor theory. Penry & Jumars (17) pointed out that most guts can be analyzed as an ideal chemical reactor of three types (or their combinations): batch reactors (e.g., the gastric cavity of a hydra or perhaps the blind-ended cecum of a rabbit), plug-flow reactors (PFRs) (e.g., the tubular intestines of many invertebrates and all vertebrates), and continuous-flow stirred tank reactors (CSTRs) (e.g., the rumen of a cow or the hindgut of a termite). They used mass-balance equations to determine the ideal gut-reactor configuration for two basic types of digestive reactions. In catalytic (i.e., enzymatic) reactions, reaction rate is a function of substrate concentration according to the Michaelis-Menten equation. In autocatalytic (e.g., microbial fermentation) reactions, reaction rate is a complex function of substrate concentration and microbe concentration. In autocatalytic reactions the maximal rate of reaction occurs at an intermediate, rather than at the highest, reactant concentration. PFRs maintain a gradient of reactant concentrations and thus a gradient of reaction rates from higher values near the reactor entrance to lower values near the reactor exit. Accordingly, Penry & Jumars (17) concluded that PFRs are a better design for digestive processes that rely on catalytic enzymatic reactions, which is why tubular guts predominate among complex, multicellular animals. However, these researchers also concluded that if, in addition to catalytic reactions, fermentation autocatalytic reactions are important, then fermentation production rate is maximized when a portion of the gut is a CSTR. These theoretical distinctions explain this review's distinction between (*a*) digesters that rely largely on endogenous enzymes to digest relatively nonrefractory materials in foods and (*b*) digesters that typically ferment relatively refractory materials with the aid of

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symbiotic microbes. Among the latter group, some species are foregut fermenters in which the microbial fermentation chamber resides proximal to the small intestine, and some are hindgut fermenters in which the fermentation chamber resides distal to the host's stomach and small intestine (2).

The gut models derived from chemical reactor theory and applied to both invertebrates and vertebrates have been useful research tools that delineate the important digestive features, show the direction and strength of the interactions of such features, and help achieve the desired integration by relating the features and their interactions to whole-animal feeding rate and extraction efficiency. Application of their basic principles can also explain why animals processing different types of food may exhibit differences in their overall digestive strategies.

The models focus attention on a few characteristics that we list here to provide context for detailed material presented subsequently: (*a*) reaction rates for substrate breakdown (e.g., by native enzymes or microbial processes) and for monomer absorption, (*b*) digesta retention time, (*c*) volume of the gut reactor or reactants, and (*d*) flow rate of digesta. As a first approximation, conversion or extraction efficiency can be expressed as

$$\text{extraction efficiency} \propto \frac{\text{reaction rate} \cdot \text{digesta retention time}}{\text{concentration of reactants} \cdot \text{reactor volume}}. \quad 1.$$

Digesta retention time can be measured using inert markers fed to both vertebrates and invertebrates (2). This equation can be used only as a first approximation because it assumes constancy in many parameters that can be relatively complicated functions of each other (see References 17 and 18 for examples of these functions). But Equation 1 illustrates that conversion or extraction efficiency should be reciprocally related to initial concentration and gut volume and positively related to both retention time and reaction rate. Food intake rate and excreta egestion rate are related to the flow rate of digesta through the gut/reactor in relation to reactor volume, which determines digesta retention time:

$$\text{digesta retention time} \propto \frac{\text{reactor volume}}{\text{digesta flow rate}}. \quad 2.$$

Thus, conversion or extraction efficiency should be reciprocally related to flow rate.

Many of these features change in coordinated fashion, enabling animals to maintain their required intake of digestible dry matter or energy when they eat foods with increasing amounts of refractory cell wall material (19). Even if animals can partially digest the refractory material, as its concentration in food increases, overall digestive efficiency declines. To compensate, they must eat increasing amounts of dry matter; to accommodate such increases, gastrointestinal tract size typically increases and/or digesta mean retention time decreases. These adjustments occur in a wide variety of endothermic mammals and birds (1, 20) and in ectotherms such as grasshoppers (21), herbivorous land crabs (15), and perhaps cockles (*Cerastoderma edule*) switched from phytoplankton to detritus (22). Integrated analysis of digestive strategy using reactor models has been usefully applied in studies with fish as well (23, 24), but other kinds of models, e.g., compartment models, are also useful (25).

Certain modes of digestion may not be well characterized by the reactor models, such as the phagocytosis and pinocytosis followed by intracellular enzymatic hydrolysis that may predominate in some invertebrates [e.g., ticks and mites (26)]. However, modeling approaches have still guided research and have enhanced understanding of many specialized features of digestion in some taxa that are not necessarily captured in the simplest reactor models. Some notable examples include (*a*) evaluation of the glandular digestion path in lamellibranch bivalves, which involves intracellular digestion, and the parallel intestinal path, which involves extracellular digestion (27), and (*b*) compartmentalization imparted by the peritrophic membrane and gel and enzyme recycling thought to occur in insects (28). The modeling approach has also facilitated the establishment

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of explicit links between suborganismal features of digestive physiology and whole-animal nutrition in production agriculture (29), links with ecological phenomena such as foraging ecology (30, 31) and community structure (16, 32), and approaches for modeling impacts of temperature change (33) that may improve predictions of animal responses to climate change (34).

Digestive System Design Is in Accord with the Economy of Nature

The digestive system is costly to run. A vertebrate's digestive tract and liver may account for 20–25% of the whole animal's respiration (35, 36). Within species, increases in size of the alimentary organs are associated with increases in basal metabolic rate (37, 38). Because of these costs, the size and performance of the digestive system should be matched to food intake and quality (2). Many examples exist of apparent economy of design in digestive features. For example, in some social ants and wasps in which adults feed larvae proteinaceous food and then ingest larval amino acid–rich excretions, the levels of protease activity in the adults' guts are extremely low (39). This seems consistent with theory because excessive capacity would waste energy and material in the synthesis of little-used proteins, and the space available for membrane-bound proteins may be limiting (40, 41). As another example, birds switched to higher-fat diets seem initially poorly matched digestively, as reflected in low extraction efficiencies (42, 43), until compensatory adjustments occur in increased digesta retention (43, 44) and in pancreatic lipase activity (45). These changes are predicted by the integrative model (Equation 1, above), which assumes that conversion/extraction efficiency declines when reactant concentration increases unless compensatory changes occur in retention time or hydrolysis/absorption rate. The alternative viewpoint is that enzymatic and absorptive capacities are in great excess relative to the typical load (i.e., the flow rate of primary nutrient) or that retention time is routinely in great excess in relation to reaction rates. But excessive retention time would limit food intake rate and be selected against in animals maximizing their growth rate or reproductive rate. In sections below, we review other examples of compensatory digestive changes that occur during acclimation to new diets and, where possible, their time courses and mechanistic and gene bases.

Considerations of evolutionary economic design suggest that enzymatic and absorptive capacities should be modestly in excess of their corresponding loads ("enough but not too much") (40, 46). Although measuring the magnitude of these matches and the corresponding spare capacity, measured as the ratio of capacity to load, raises a number of problems (47, 48), estimates by a variety of methods (47, 48) imply that immediate spare capacity (i.e., prior to any acclimation or acclimatization) is less than two.

MATCHES ACHIEVED BY NATURAL SELECTION BETWEEN DIETS AND DIGESTIVE SYSTEMS

On the basis of arguments of the economy of nature (above), animals adapted to particular diet features ought to exhibit several patterns. For dietary components such as nonstructural carbohydrates (e.g., sugars, starch), protein, and lipids, there should be a positive relationship between their level in the natural diet and the presence or number of gut enzymes and transporters necessary for their breakdown and absorption (2, 49). For low-quality foods with relatively high levels of refractory material (e.g., structural carbohydrates), larger or longer guts should allow for higher intake while still maintaining adequate retention time for breakdown and absorption (50).

An earlier review of scores of investigations in many taxa identified patterns that were consistent with these predictions (1). For example, many of the carbohydrate-degrading enzymes are correlated positively with dietary carbohydrate level in fish (1), birds (1), mammals (1), crustaceans (51–53), oligochaetes (54), and possibly insects (55). Herbivores tend to have more voluminous digestive tracts than do carnivores

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of the same size in the cases of fish (56, 57), mammals (2, 6), birds (2, 6), reptiles (2, 6), amphibians (2, 6), and insects (55). Although in total these studies are consistent with the adaptational hypotheses, subsequent work has strengthened the analysis, as the paragraphs below review.

Correlated Evolution of Diet and Digestive Features

Since the earlier review (1), the literature has expanded with the inclusion of information on new taxa of animals, especially invertebrates, and new diets. These include mites that consume plant materials and have higher levels of glycosidases (examples in **Table 1**) than do those that live on animal secretions or blood (26), which is a pattern analogous to the above-described correlation between carbohydrate-digesting enzymes and dietary carbohydrate. Other mites that eat and grow on bacteria have higher activity levels of lysozyme, which breaks down bacterial cell walls (58).

A second feature that strengthens the analysis is more uniform methodology, including phylogenetically informed statistical analysis. Earlier studies, by contrast, were sometimes two-species comparisons, which obscure inference about correlated evolution of diet and physiological traits (59). Inclusion of phylogenetic considerations [e.g., by phylogenetically independent contrasts (60)] can improve the analyses because species closely related by evolutionary descent are treated as not statistically independent (2). Also, researchers on digestive systems of insects (61) and fish (62–64) have emphasized that formal incorporation of phylogenetic relationships in comparative studies can reveal important biological information (e.g., phylogenetic signals and constraints) and pattern(s) of dietary specialization.

Recent studies with fish, birds, and mammals exemplify these improvements. German et al. (65) constructed a phylogeny for 10 minnow species (family Cyprinidae) and incorporated it into their tests for digestive system matches to diets composed of varying amounts of animal, algal, diatomaceous, and detrital material. Herbaceous taxa had longer digestive tracts and higher activity of the carbohydrases amylase and laminarinase in their guts, whereas insectivorous species had higher chitinase activites. The latter pattern had not been apparent in previous surveys of fish species, but those surveys had not focused on closely related species that lack large differences in gut size and predigestive mechanical processing that can confound the analysis (65).

Schondube et al. (66) used a phylogeny for New World bats (family Phyllostomidae) to analyze the correlation between diet and digestive enzymes in 14 species. They used the ^{15}N level of the bats' blood to characterize their diets, which were composed of insects, nectar, fruit, or blood. They made 20 a priori predictions about patterns in sucrase, trehalase, maltase, and aminopeptidase N. Amazingly, all 20 a priori predictions for these enzymes were borne out. For example, a shift from insectivory to sanguinivory and carnivory (i.e., the reduction of insect trehalose in the diet) was accompanied by a 10- to 15-fold decrease in trehalase activity. A shift from insectivory to nectarivory or frugivory (the addition of plant sugars to the diet) was accompanied by a significant increase in maltase and sucrase activity, a decrease in trehalase activity, and no change in aminopeptidase N activity (because bats in all diet groups digest protein). The probability of such high concordance with predictions is so infinitesimally low that the authors concluded that evolutionary changes in diet in phyllostomid bats were indeed accompanied by adaptive shifts in digestive enzymes.

Phylogenetically informed analyses of digestive enzymes in birds have revealed both dietary and phylogenetic influences. American robins and other closely related species such as European starlings and gray catbirds, all members of the large (≈600 species) and monophyletic sturnid-muscicapid lineage, lack intestinal sucrase activity (67). Among other passerine birds that do express sucrase-isomaltase, sucrase activity is 10 times higher in the hummingbird lineage (family Trochilidae), even when

Phylogenetically independent contrasts: a statistical method that uses information on phylogenetic relationships to assess evolutionary correlations between traits

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SGLT1: sodium-dependent glucose transporter 1

compared with other nectar-consuming passerine birds (68). But hummingbirds are unremarkable in regard to the activity of other enzymes such as maltase and aminopeptidase N. Maltase activity appears to have a strong dietary influence among bird species. Nectarivorous and omnivorous species have higher maltase activities compared with insectivorous species (69). This pattern, as well as an analogous pattern for pancreatic amylase, was recently confirmed in a phylogenetically informed comparison among six passerine species that consume diets with differing amounts of starch (70).

Generally, in vertebrates, the more carnivorous the species, the lower is the rate of intestinally mediated glucose absorption (1). This pattern, first described in a survey of more than 40 species drawn from the major vertebrate classes (49), is also apparent in comparative studies within fish (71) and birds (72). On the basis of phlorizin-binding studies in a limited number of species, species differences in tissue-specific glucose uptake may largely reflect species differences in copy number of the main apical membrane glucose transporter SGLT1 (sodium-dependent glucose transporter 1), although differences in transporter turnover time may also contribute (73).

There was no marked pattern of higher intestinal transport activity for amino acids among the more carnivorous vertebrate species (1, 49). Likewise, for digestive enzymes, carbohydrases and dietary carbohydrate typically are positively related, but proteases/peptidases and dietary protein are not, at least for fish (65) and birds (70). This finding is expected because all animals, regardless of diet, need protein, so selection should not be strong for very low protein-processing capability in animals. Additionally, Hofer & Schiemer (74) argued that herbivores with relatively rapid gut throughput should have compensatorily higher biochemical capacity to process and recover proteins rather than to excrete them. The correlated evolution of diet and digestive features can be studied by experimental evolution. After flour beetles were raised over 13–16 generations on diets with different contents of starch and other components, amylase activity was significantly higher in such flour beetles than in controls raised on the standard diet (75).

Molecular Mechanisms for Differences in Enzyme Activities Between Populations/Species

Information has expanded on changes in particular genes and proteins responsible for differences in digestive capacity. A good example concerns changes in carbohydrases coincident with the inclusion of starchy foods and milk products in the human diet. In the case of starchy foods, the focus has been on salivary amylase. The salivary amylase gene *Amy1* is an isoform distinct from the pancreatic amylase gene *Amy2*, from which *Amy1* originated by duplication (76). The functions of *Amy1* may be (*a*) to augment pancreatic amylase activity (salivary amylase persists in the stomach after swallowing) or to initiate starch breakdown in the mouth and thus either (*b*) to speed glucose absorption or (*c*) simply to release sugars for tasting and thus help in the identification of nutritious (starchy) foods (76, 77). In humans sampled by Perry et al. (77), there was a positive correlation between *AMY1* gene copy number (ranging from 2 to 14 copies) and milligrams of AMY1 protein per milligram of saliva (ranging from <0.2 to ~ 6). Perry et al. found that copy number was significantly higher in the three high-starch populations studied than in the four low-starch populations studied. The populations were geographically widely distributed, and the interpopulation variation in copy number was related most strongly to diet and not to geographic proximity. Furthermore, *AMY1* copy number and salivary amylase protein levels in humans generally are at least three times higher than in chimpanzees and bonobos, whose diets are composed predominantly of fruit and leaves, which contain much less starch than the diets of most human populations. The picture that emerges is one of correlated evolution of diet and amylase coincident with the dietary shift early in hominin evolutionary history toward starch-rich plant

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underground storage organs such as bulbs, corms, tubers, and later grains.

Only mammals produce milk. Its primary carbohydrate in most species is lactose. Lactose is hydrolyzed by the membrane-bound intestinal enzyme lactase-phlorizin-hydrolase (or lactase, for simplicity), which is encoded by the lactase gene (*LCT*). In most mammals lactase activity is high at birth and declines sharply around weaning. Ingestion of large amounts of lactose after that normally results in the escape of undigested lactose to the distal gastrointestinal tract, where it is fermented, leading to the production of gases (CO_2, H_2, and methane) and osmotic diarrhea. The majority of humans are lactose intolerant, but members of a small number of populations that have been associated historically with domestic ungulates (cows, sheep, and goats) are lactose tolerant. Single-nucleotide polymorphisms (SNPs) explain these differences. The first evidence for SNPs as causative factors in lactose intolerance came from a study of Finnish families in which a DNA variant (C/T_{-13910}) located in the enhancer element upstream of *LCT* was associated with lactose intolerance (78). The allele that carries the T_{-13910} variant was subsequently found to correlate with lactose tolerance in many global populations, and a variety of functional studies have revealed some of the molecular steps by which the allele controls lactase expression in intestinal cells (79). However, some populations (e.g., in sub-Saharan Africa and Saudi Arabia) that lacked the variant T_{-13910} nonetheless had a high prevalence of lactose tolerance. Subsequently, researchers identified other SNPs that correlated with lactose tolerance, and analyses seem to indicate that convergent evolution of the phenotype occurred a number of times at a number of different locations (79). On the basis of genetic patterns and analysis of Neolithic human skeletons, the ancestral human condition appears to be lactose intolerance in adults, but in a number of locations (i.e., cultures), humans' consumption of dairy products created a strong selection pressure for the evolution of genes that support adult lactose digestion (76).

Genetic variants of amylase have been described in some invertebrates such as molluscs (80, 81) and several insect species (82–84). Research on these systems indicates that the enzyme gene polymorphisms may be nonneutral and may give important advantages in processing diets and in turn beneficial rewards for growth and/or reproduction to individuals carrying certain genotypes, although the details of these scenarios are not as well established as in the aforementioned examples based on research in humans.

MATCHES ACHIEVED BETWEEN DIETS AND DIGESTIVE SYSTEMS BY PHENOTYPIC FLEXIBILITY

We discuss above some expectations and patterns for animals that switch among diets differing in amounts of refractory material. On the basis of arguments of economic design (above), one might predict that for an omnivore switching among diets with differing amounts of hydrolyzable carbohydrates, protein, and lipids, there will be a positive relationship between dietary substrate levels of gut enzymes and transporters and the number of such enzymes and transporters necessary for nutrient breakdown and absorption. However, not all animals should be expected to modulate enzyme and transporter levels, especially if there are costs involved. The benefit of phenotypic flexibility, and therefore selection for it, is low or nil in animals, like carnivores, that do not switch diets or that switch between diets that differ little in substrates. In cats, for example, addition of carbohydrate to the diet has little effect on either pancreatic amylase activity (85) or SGLT1 activity (86), in contrast to the substantial inductions that occur for both enzymes and transporters in rodents (e.g., rats and mice) and fish (e.g., trout and tilapia) (1). In the following sections, we briefly review such patterns, extend them where possible to include invertebrates, and discuss current knowledge about the mechanistic bases of such patterns.

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Paracrine mechanism: chemical signaling in which the target cell is close to the signal-releasing cell

CDX2: caudal-type homeobox transcription factor 2; encoded by the *Cdx2* gene

Caudal-type homeobox: DNA sequence that codes for homeodomain proteins that have transcription factor activities

Hepatocyte nuclear factor 1 (HNF1): transcription factor that regulates the expression of a wide variety of target genes and binds to DNA as homodimers

CREB-binding protein: ubiquitously expressed transcriptional coactivator with intrinsic histone acetyltransferase activity

Enzymatic Activity Is Flexible

Earlier review of scores of investigations in many mammals, birds, and fish identified patterns that were consistent with the predictions that major pancreatic enzymes (proteases, amylase, lipase) and intestinal brush-border enzymes (aminopeptidase N, sucrase, maltase) change in proportion to the dietary content of their respective substrates (1, 2). A recent study (87) showing induction of pancreatic α-amylase specific activity (a twofold increase) in the lizard *Teius merianae* fed a 30% starch diet (compared with *T. merianae* fed a 0% starch diet) adds reptiles to the list. Analogous induction of amylase activity by dietary carbohydrate has been demonstrated in insects (88, 89) and crustaceans (90–92). Protease activities also increase on a higher-protein diet in some cases in insects (93), crustaceans (90), and cephalopods (94). In almost all other taxa, these capabilities remain to be explored.

Mechanisms of Modulation of Enzyme Activity

Food chemicals strongly regulate digestive enzyme activity through direct effects on cells and/or paracrine mechanisms in both vertebrates (1) and insects (95). Mechanisms underlying dietary flexibility of intestinal enzyme activity have been studied mostly in laboratory rodents but also in a few other species. Stimulation of carbohydrase and aminopeptidase activities in rodents, which is apparent within a day of a diet switch, appears to be due largely to a more rapid protein synthesis rate (1, 96–100). In nestling house sparrows fed a 25% starch diet, compared with a starch-free diet, an increase in maltase-glucoamylase mRNA was correlated with an observed increase in maltase activity (101).

Carbohydrase expression is regulated by transcriptional factors' binding to promoter/enhancer gene regions [e.g., CDX2 (caudal-type homeobox transcription factor 2) and HNF1 (hepatocyte nuclear factor 1)] and by acetylation of histones associated with the recruitment of the mRNA transcriptional complex on the promoter/enhancer and transcriptional gene regions (98, 102, 103). Mochizuki et al. (98) observed in mice that the induction of the maltase-glucoamylase gene expression by a high-sugar diet is associated with an increase in (*a*) binding of CDX2 and HNF1 to the promoter/enhancer gene region; (*b*) acetylation of histones (in particular that of histone H3 at K9); and (*c*) binding of CREB-binding protein to promoter/enhancer and transcriptional gene regions. Likewise, an increase in acetylation of histones H3 and H4 occurs for sucrase-isomaltase in mice fed a high-starch diet (102). Several studies show that both transcriptional and posttranscriptional events regulate pancreatic digestive enzymes (1, 89, 104).

Unexpected Patterns

Some observations do not fit neatly into the patterns that we describe above. For example, adult pigeons and adult birds in the order Passeriformes (five species) have not shown induction of intestinal carbohydrases on a high-carbohydrate diet (105; but see Reference 106 for a lone exception), although they do show induction of aminopeptidase N on a high-protein diet. To make things more mystifying, the opposite seems to be the case for galliform and anseriform birds in which intestinal carbohydrases are modulated but peptidases are not (105)! *Xenopus laevis* (African clawed frog) also does not conform to the general model of adaptive dietary modulation of carbohydrases (107). Studies involving the costs and benefits of modulation and/or the effects of age and phylogeny may be needed to make sense of these patterns.

Another puzzling observation is the occasionally observed mismatch between a dietary substrate level and the induction of an enzyme activity. A protein-rich diet reduced sucrase activity in rats, and high-fat diets lowered carbohydrase activity in rats (108) and some birds (106, 109). In these cases the reduced carbohydrase activity was not associated with reduced dietary carbohydrate. Researchers

have proposed that high-protein diets may increase pancreatic proteases in the intestinal lumen, which increase microvillar degradation, and that brush-border enzymes (e.g., sucrase) that protrude most into the lumen are more exposed to proteolysis (108). As for high-lipid diets, in rats, high fat reduced the activities of maltase, sucrase, and isomaltase and concomitantly reduced sucrase mRNA and protein levels (102). In addition, sucrase-isomaltase has *N*- and *O*-linked glycosylated chains, and glycosylation inhibition reduces the transfer of the protein to the apical membrane of the enterocyte (references in Reference 110), suggesting the importance of sucrase-isomaltase glycosylation for expressing the enzyme complex at the brush-border membrane. In rats fed a high fat-to-carbohydrate-ratio diet for 14 days, Mochizuki et al. (110) observed that the reduced ratio of jejunal sucrase activity to isomaltase activity was associated with the reduction of unsialylated galactose from the glycosylated chain of sucrase-isomaltase, perhaps limiting the mobilization of the enzyme complex to the apical cell membrane and reducing the complex's activity. Whether the effect of lipids on carbohydrases has a biological meaning or is just a side effect is unknown and begs for further clarification.

Transport Activity Is Flexible

Food regulates the activities of many intestinal nutrient transporters (111). Unlike the case for digestive enzymes, we should not always expect positive relationships between nutrient transporter activity and dietary substrate levels (112). Transporters for monosaccharides and amino acids/peptides, all of which can be used to meet energy needs, should tend to be upmodulated by their substrates (dietary carbohydrate and protein, respectively). In contrast, transport of an essential water-soluble vitamin or mineral should be downmodulated by its substrate and upmodulated in deficiency because such a transporter would be most needed at a low dietary level and least needed at a high level, when requirements might be met by passive diffusion down a concentration gradient. Avoidance of toxicity might be another benefit of downward modulation of some minerals (e.g., iron) and amino acids (113) at a high dietary level.

Ferraris & Diamond (114) reviewed the contrasting patterns for dietary effects on intestinal apical uptake of sugars, dipeptides and amino acids, minerals, and vitamins. The studies were performed mostly in laboratory rodents, and additional studies in other vertebrates are described below, but we do not know of analogous studies in invertebrates. As predicted, dietary carbohydrate stimulates brush-border aldohexose uptake, and dietary protein or amino acids stimulate amino acid and dipeptide uptake. Also as predicted, intestinal absorption rates for minerals are modulated downward by high dietary levels and upward by low levels. Uptake of essential amino acids was maintained or even slightly enhanced in deficiency, and thus their modulation at low dietary levels was more similar to that of essential nutrients than to that of the nonessential amino acids aspartate and proline. Modulation of the latter amino acids can occur semi-independently of the essential neutral and basic amino acids because there are semiprivate amino acid transporters for imino and acidic amino acids.

Modulation of vitamin transport is partly but not entirely consistent with the a priori predictions. Biotin and thiamine transporters are upmodulated in the absence of their substrates, and biotin transport is downmodulated by its substrates, but transport of pantothenic acid, ascorbic acid, and choline is, for the most part, not modulated by their dietary levels (115). Stein & Diamond (116) suggested that modulation of a vitamin may not occur if a large proportion of the vitamin's absorption is passive and hence modulation of mediated absorption is not important. The uptake kinetics of pantothenic acid, ascorbic acid, and choline indicate that mediated uptake makes a smaller contribution to total uptake compared with the uptake pattern of other vitamins whose transport is upmodulated in deficiency. As we see below, this same logic can be used to explain

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why most birds do not modulate sugar absorption in the predicted pattern.

Four studied omnivorous bird species failed to modulate mediated sugar absorption (117), but small birds exhibited considerable passive absorption compared with nonflying mammals (118). Pappenheimer (119) suggested that passive absorption may confer a selective advantage because it requires little energy and provides a mechanism by which absorption rate is matched to luminal substrate concentration or hydrolysis rate. As discussed above for vitamins, matching between the capacity for mediated absorption and dietary substrate level is not necessarily predicted if most absorption occurs by a passive pathway (116). Although passive absorption may be seen to be less costly than transporter-mediated absorption, the former may be less selective than the latter and may permit water-soluble xenobiotics to be absorbed from plant and animal material (40). This vulnerability to toxins may explain why many animals do not rely on passive absorption of water-soluble compounds and why, for those that do, such vulnerability may be an important ecological driving force, constraining exploratory behavior, limiting the breath of the dietary niche, and selecting for compensatory behaviors such as searching for and ingesting specific substances that inhibit hydrophilic toxin absorption (120).

Mechanisms of Transport Activity Modulation

Molecular studies of the modulation of intestinal sugar absorption indicate that it is achieved largely by increasing and decreasing the apical membrane density of transporters for glucose (SGLT1) and fructose (GLUT5) by altering transcription rates (1). In horses habituated to diets with higher hydrolyzable carbohydrate, glucose transport rates, SGLT1 protein content, and SGLT1 mRNA expression were two times higher in the jejunum and three to five times higher in the ileum (121). Much of the response to a new dietary signal like higher or lower dietary glucose content occurs in the newest cells that are born in the crypts and migrate up the villus length, finally to be shed into the lumen. In a lab rodent, the cell population of the whole length of the villous is renewed in 1 to 2 days, which therefore determines the time for complete diet adjustment. Some response times to altered dietary glucose can be much faster; one example is the movement and insertion of GLUT2 glucose transporters into the brush border, upon the presence of luminal sugar, over only a few hours in rats (122).

The products of protein digestion (dipeptides, tripeptides, amino acids) are signals for increasing the gene expression of Pept-1, leading to increased population of the peptide transporter in the intestinal brush-border membrane. Transactivation is mediated through the presence of an amino acid–responsive element in the promoter region of the *Pept1* gene (123, 124). Other pre- and posttranscriptional mechanisms regulating peptide transport activity have been described (125, 126).

THE MULTIGENOMIC PHENOTYPE: DIGESTIVE ECOLOGY AND THE MICROBIOME

Only in part is digestive performance determined by the animal's own genome and by the interaction of this genome and the environment. The multiple genomes of the gut microbiota are also relevant (127, 128). This complementary perspective emerges from molecular characterization of the diversity of microbes in the gastrointestinal tract (the gastrointestinal microbiome) and their inferred metabolic capacities (129). The human gut microbiota contains up to an order of magnitude more cells (100 trillion cells) than the host, and these bacterial cells encode two orders of magnitude more unique genes than the human genome (130). Two technological advances that opened this new frontier in biology and continue to propel the field are analysis of 16S rDNA data and metagenomics (129). The former documents the taxonomic and phylogenetic diversity of the microbiome, and

Xenobiotics: chemicals found in an organism not normally produced or expected to be present in it (e.g., antibiotics and many human-made toxins)

Microbiome: all microbes, their genomes, and their environmental interactions in a well-defined environment

16S rRNA: a component of the 30S subunit of prokaryotic ribosomes

Metagenomics: the study of metagenomes, which comprise the genomes found within a microbiome

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the latter infers metabolic capacity from genes in the microbiome. In this section, we briefly review a few themes of the rapidly growing literature on the biology of gastrointestinal microbiomes. We consider the correlation between diet and the characteristics of the microbiome, the potential mechanisms that lead to microbiome differences, and the functional consequences of these differences for hosts.

Diet and the Characteristics of the Microbiome Appear to Be Correlated

A dominant theme in digestive ecology is the correlation between the physiological and morphological features of the digestive tract and diet. Accordingly, we can ask whether diet has an influence on the diversity, taxonomic composition, and metabolic capacity of the microbiome. Following the strategy of comparative physiology, we can ask this question at the complementary levels of species or individuals. Ley et al. (131) conducted an extensive study of the diversity of the microbiomes of 54 mammal species. They found that bacterial diversity was lowest in carnivores, intermediate in omnivores, and highest in herbivores (132). This pattern appears to hold independently of phylogenetic level of analysis: Herbivore guts appear to have the highest diversity of bacterial phyla and operational taxonomic units (OTUs) at all levels. Microbiologists define OTUs by sequence similarity at a certain level (133). For example, organisms with sequence identity in which all 16S rRNA gene sequences are at least 97% identical are often considered to define a species, and those with at least 95% sequence identity are considered to define a genus (134). OTUs are sometimes referred to as phylotypes.

The phylogenetic affinities of microbiome members seem to differ among animals, depending on diet and gut type. Thus, hindgut fermenters have phylogenetically similar microbiomes that differ from those of foregut fermenters and from those of animals with simpler guts [monogastrics (131)]. These associations are not without exceptions, however. The correlation between diet, gut morphology, and the phylogenetic affinities of the microbiome's bacterial taxa is confounded by covariation between diet, digestive morphology, and the hosts' phylogenetic relationships. For example, in spite of their herbivorous habits, red and giant pandas (*Ailurus fulgens* and *A. melanoleuca*) have simple guts with relatively reduced microbiomes that are more similar to those of phylogenetically related carnivores. In contrast, omnivorous humans have microbiomes that are more similar to those of fruit-eating bonobos (*Pan paniscus*) and lemurs (*Eulemur macaco* and *Lemur catta*) than to those of chimpanzees (*Pan troglodytes*) (131, 132). Sometimes diet has an overriding influence on the microbiome's structure, but sometimes common ancestry overrides the effects of diet. The relatively small sample of mammals studied to date does not yet elucidate the relative influence of diet and gut morphology on microbiome structure when phylogenetic relationships are accounted for. To our knowledge, research on the phylogenetic similarity of mammalian microbiomes has not been accompanied by comparative metagenomic studies of similar scope. Consequently, whether the patterns in diversity and composition revealed by 16S rRNA studies are mirrored by patterns in the metabolic capacities of mammalian microbiomes is still unknown.

Ley et al. (131) have hypothesized that the differences among taxa are the result of coevolution between microbiome members and hosts. This hypothesis is sensible and exciting because it extends the idea of correlated evolution between digestive features and diets to the microbial world that lives in symbiotic association with animals. Attractive as this idea is, much remains to be done to test it critically. Reciprocal transplants of microbiomes across phylogenetically distant hosts reveal a low degree of microbe or host specialization. When microbiomes from zebra fish and mice are reciprocally transplanted into germ-free hosts, they change in composition but eventually reach states that seem to function adequately well (135). Germ-free mice inoculated with human microbiomes also develop functional gut

Operational taxonomic units (OTUs): units defined by sequence similarity because most bacteria cannot be cultured

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Mutualism: biological interaction in which each individual derives a benefit

microbial communities (136). We speculate that reciprocal evolution between hosts and gastrointestinal microbes takes place at high phylogenetic levels and does not involve high degrees of host-microbe species-to-species specialization. If this speculation is correct, it explodes the notion that a close degree of intimacy between mutualistic patterns is always accompanied by a high degree of exclusivity and specialization (137).

There May Not Be a Core Phylogenetic Microbiome

The patterns described above suggest consistent differences among mammalian species. The microbiomes of conspecifics tend to resemble one another in diversity and phylogenetic composition more than those of other species (131). This statement does not imply that conspecifics' microbiomes are identical. Indeed, species' phylogenetic core microbiomes have proven elusive, even in the best-studied species. For example, Tap et al. (138) studied the microbiome of 17 humans and found that most OTUs (78.6%) were specific to a single individual. Only a small minority of OTUs (2.1%) was shared by 50% of individuals, and not a single OTU was shared by all individuals. A large study of human twins arrived at a similar result (139). Although the microbiomes of twins were more similar to each other than to those of unrelated individuals, members of twin pairs had microbiomes as distinct as fingerprints—but not nearly as temporally stable (140). In one of the few studies of wild animals, Godoy-Vitorino et al. (141) studied the microbiomes of the fermentative crop of six hoatzins (*O. hoazin*) and found very little overlap in composition. The vast majority of species-level OTUs (≈70%) were unique to each individual: All six individuals shared only one OTU. These observations led Turnbaugh et al. (139) to conclude that the hypothesis of a core human microbiome definable by a set of abundant microbial OTUs is probably incorrect.

There May Be a Core Metagenomic Microbiome

Beta diversity characterizes how species composition varies from ecological community to ecological community (142). The microbiomes of vertebrate guts have beta diversities much higher than those of macroscopic ecological communities (142). This outcome is dependent on the resolution of the marker used to characterize microbial species (sequence similarity in 16S rRNA). Other markers and deeper sampling may change the current perspective of considerable interindividual diversity of almost innumerable bacterial species (143). The seemingly remarkably high beta diversity of vertebrate gut microbiomes might suggest that these ecological communities are functionally very different, but this seems not to be the case. Metagenomic research has revealed remarkable similarities in the genes present in the microbiomes of the best known species: humans and laboratory mice. Instead of a core microbiome defined by species, there may be a species-specific microbiome defined by a collection of shared genes that specify a common set of metabolic capacities (139). A corollary of the hypothesis of a core metagenome is that microbiomes of host species with similar diets will share metagenomic cores, in spite of likely large differences in microbial species composition. Documenting these core metagenomes in a variety of species with contrasting diets will illuminate the potentially different functional roles that different microbiomes play for hosts.

Using an ecological analogy, we can view the microbiomes of a single species as ecological communities inhabiting hosts/islands. The pool of potential colonists to these islands is potentially very large, and there is much functional/niche redundancy in these species (144). Thus, the observed patterns of diversity in these islands resemble communities assembled by a combination of neutral and idiosyncratic processes (145, 146). This view does not imply that gut microbiomes have no admission requirements. Microbiomes are characterized by high diversity represented by hundreds of species

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and thousands of strains but by very low diversity of deep lineages (144). Among mammals, microbiomes include members of at most 6 bacterial phyla (147). In contrast, soil samples can contain up to 20 phyla (148). Typically, a microbiome is dominated by species from only 1 or 2 phyla. Among mammals a common dominant phylum is Firmicutes, but in some mammalian taxa Bacteroidetes, Proteobacteria, and Actinobacteria can dominate (131). The ecological processes that filter and sort the microbial taxa that end up in a microbiome appear to work at high phylogenetic levels. Ecological factors that influence the inclusion and persistence of taxa within a microbiome, and hence potentially the microbiome's function, include the potential pool of colonists (139), the host's diet (136), the immune factors that mediate host-microbe interactions (149), and the interactions among microbes within the microbiome (150).

Dietary Modulation of the Microbiome

In most animals with well-developed microbiotas, diet changes are accompanied by changes in microbiome diversity, composition, and function. Turnbaugh et al. (136) switched mice with relatively homogeneous microbiomes from a plant-based, low-fat diet to a sugar- and fat-rich diet that resembles Western human diets in nutrient content. Within 24 h the phylogenetic composition of the microbiome changed. These changes in the phylogenetic composition of the microbiome ceased after approximately 7 days and were accompanied by large changes in the composition of both the array of microbiome's genes and its transcriptome. The diet change also led to a large increase in hosts' fat content. Both Turnbaugh et al.'s (139) study and a similar study conducted by Hildebrandt et al. (151) documented a significant change in the relative representation of bacterial phyla (a decrease in Bacteroidetes and an increase in both Firmicutes and Proteobacteria). Similar studies of cows [*Bos taurus* (152)] and dogs [*Canis lupus familiaris* (153)] yielded equivalent results: The remaining unanswered question is whether these changes have consequences for the digestive and metabolic performance of the hosts.

Are the Host's Genome and the Microbiome's Metagenome Complementary?

Relative to prokaryotes, eukaryotes have limited metabolic abilities. Throughout the history of life, eukaryotes have acquired novel metabolic capacities by establishing symbiotic relationships with prokaryotes [reviewed by Karasov & Martínez del Rio (2)]. The association between hosts and their digestive microbiomes appears to have led to the functional complementarity of the host's genome and the microbiome's metagenome. The microbiomes of ruminants and termites allow these animals to use the most abundant polymers on earth [reviewed by Karasov & Martínez del Rio (2)]. Such an association also allows them to recycle nitrogen, to transform poor-quality dietary nitrogen into high-quality dietary protein, to detoxify xenobiotics (154), and to reduce the need for a variety of essential nutrients (155). The interaction of the genome and the metagenome is well illustrated by the gene expression changes and by the profound physiological changes that take place when germ-free animals are inoculated with a normal microbiota (156, 157). In a massive effort, Qin et al. (130) characterized 3.3 million nonredundant genes from the microbiomes of 124 humans. They concluded that the shared human minimal (or core) metagenome includes a staggering number of metabolic functions (≈6,313). A number of the metabolic capacities encoded in the human gut metagenome are absent in hosts (130). The microbiome adds not only metabolic capacities but also flexibility to the multigenomic phenotype. For example, Hehemann et al. (158) documented the ability to hydrolyze the complex polysaccharides of marine algae in a bacterium that is commonly found in the human gut (*Bacteroides plebeius*). This ability was likely acquired laterally from marine bacteria ingested accidentally and

Transcriptome: the set of all RNA molecules produced in one cell or a population of cells

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facilitates the assimilation of dietary algae (eaten as nori) by the bacterium and presumably by its hosts. Qu et al. (159) suggest that mobile DNA elements are a major functional component of gastrointestinal microbiomes, thus contributing to horizontal gene transfer and functional microbiome evolution. The genetic promiscuity of bacteria gives the multigenomic phenotype a potential source of metabolic innovation unavailable to the host alone.

Because the multigenomic phenotype results from the interaction between the microbiome and the host, it can be difficult to track the causation pathway for a given trait; the traits of hosts and microbiomes have reciprocal influences. Considerable effort has been placed on microbiome traits related to obesity in mice and humans (160). In laboratory mice, obese and lean individuals differ in microbiome composition and on its metagenome [reviewed by Ley (160)]. When germ-free mice are inoculated with microbiomes from obese individuals, they gain more weight in the short term than do mice inoculated with microbiomes of lean mice [reviewed by Ley (160)]. Whether these effects are persistent is unclear. In humans, obesity seems to be associated with lower phylum-level diversity in the microbiome, changes in composition (reduced Bacteroidetes and increased Firmicutes abundance), and increased representation of carbohydrate and lipid metabolism genes in the metagenome (160). The microbiome's characteristics are influenced by a host of factors, including the host's genetics (161), vertical transmission of microbiome members from mother to progeny (reviewed by Reference 162), and diet (151). Any, or all, of these factors and their potentially complex interactions can cause both body weight regulation and the microbiome characteristics that correlate with such regulation. Because a variety of factors influence both the microbiome and the host's phenotypes, it is difficult to disentangle causes from consequences on the basis of correlations alone or even experiments. The microbiome of mice and men influences energy storage, but it is likely that the host's traits are also important and interact with those of the microbiome in producing the multigenomic digestive phenotype.

Digestive Ecology's Approach Has Much to Offer to the Study of Microbiomes

With very few exceptions (see References 131 and 163), recent research on the microbiome has emphasized a small subset of hosts: humans and laboratory model organisms. This emphasis is understandable and has been fruitful, but it has limitations. The causes and consequences of the reciprocal evolution of the interaction between hosts and members of the microbiome are probably best understood and interpreted in a variety of wild animals choosing and eating wild foods. Inbreeding and selection for performance in a laboratory environment, including homogeneous high-quality diets, are likely to have led to significant changes in the microbiomes of model organisms (164, 165). In addition, laboratory conditions (inactivity and ad lib feeding) seem to have a strong influence on the physiology of laboratory animals (166). To our knowledge, the characteristics of the microbiome of wild *Mus musculus* (or wild zebra fish) have not been compared with those of their laboratory brethren. Humans are the only animals that rely on cooking to transform the nutritional and digestive properties of food (167). From a nutritional perspective, we are a peculiar organism, and we likely have a peculiar microbiome—much like laboratory model organisms. Digestive ecology's broad comparative approach can facilitate the answering of important questions about the gastrointestinal microbiome. Specifically, this approach can help to elucidate the factors that have shaped the traits of the microbiome, including its size, its diversity and composition, and the expression of its metagenome (131). The emphasis of digestive ecology on whole organisms can also help us to understand the effect of the microbiome on hosts' digestive performance and on the evolution of hosts' response to microbiome changes.

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The functional complementarity hypothesis implicitly assumes that the relationship between at least some components of the microbiomes and the host is mutualistic (134). This is undoubtedly the case, but so is the notion that other components of the microbiome are commensals and others might be parasitic—the microbiome is a complex society. What we commonly assume is that in toto the gut microbiome provides a nutritional benefit to the host. We assume that the hosts gain carbon, energy, and sometimes high-quality nitrogen and essential nutrients. In turn, the members of the microbiome receive food and anoxic shelter (2). From the perspective of digestive ecology, we must consider the assumption of mutual benefit a testable hypothesis rather than an established fact. For example, documenting the presence of genes that hydrolyze the complex polysaccharides in sea algae in *B. plebeius* (158) implies that the bacterium can hydrolyze these substances. This finding does not imply that the host receives a direct nutritional benefit (168). In a similar fashion, although the biosynthetic pathways for most indispensable amino acids are found in the bacteria of the human gut (130), it has proven remarkably difficult to document the extent and mechanisms of transfer of these nutrients from bacteria to host (169).

The maintenance of mutualistic interactions depends on the balance of costs and benefits for all partners involved (170). To our knowledge, the microbiome's contribution to the multigenomic phenotype's total energy expenditures has never been quantified. Two lines of evidence suggest that this cost is significant. First, antibiotics seem to promote growth and feed use efficiency in domestic pigs (*Sus scrofa*) and chickens (*Gallus gallus*) (171). Although the mechanisms of this effect remain unclear, antibiotics are believed to reduce the competition between bacteria and host for rapidly digestible nutrients and to reduce the turnover of the hosts' mucosa and hence decrease the costs of maintaining the gastrointestinal tract [reviewed by Gaskins et al. (172)]. The second line of evidence is the wide variation in the sizes of the gastrointestinal chambers that house microbes observed in animals (2). The cost-benefit balance for the host depends on diet, which is probably why we observe such wide variation in the sizes of the digestive tract sections that house the microbiota and why most animals with herbivorous diets have guts with capacious fermentation chambers whereas carnivores have either no fermentative chambers or greatly reduced ones (173). Humans have guts that are only approximately 60% of the size expected of an anthropoid primate (174). In other hominid apes, the colon represents ≈52% of the total volume of the gastrointestinal tract. In humans, the colon represents from only 17% to 20% of the total volume of the gastrointestinal tract (174). Wrangham & Conklin-Brittain (167) speculate that the differences in gastrointestinal form and function between humans and great apes are the consequences of humans' adaptation to eating cooked foods. Cooking tenderizes food, increases the bioavailability of a variety of nutrients (including starch and proteins), decreases the toxic content of food, and reduces the insoluble fiber content of food (175). An interesting question is whether we can detect the evolutionary effect of major dietary changes, such as those that have resulted from cooking, on the microbiome and its functional capacity. The complementary question is how hosts have responded to diet-related evolutionary changes in the microbiome. These questions highlight the enormous potential of research at the intersection of digestive ecology and the biology of microbiomes.

SUMMARY POINTS

1. The morphological and functional design of gastrointestinal tracts can be explained largely by the interaction between the chemical constituents in the diet and principles of economic design, both of which can be embodied in chemical reactor models of gut function.

2. Natural selection seems to have led to the expression of digestive features, including the activity of digestive hydrolases and transporters, that approximately match digestive capacities with dietary loads while exhibiting only relatively modest excess.
3. Evolutionary forces have selected for animals with digestive features tailored to effectively process one or a few features of foods and substrates and have not selected for animals that can effectively process all of them at the same time ("jack of all trades, master of none").
4. Evolution has made use of copy number variations and single-nucleotide polymorphisms as sources of phenotypic variation in digestive biochemistry among populations and/or species.
5. The traits of the gastrointestinal tract are phenotypically flexible, but the degree of flexibility depends on the complex interaction between taxa and nutrients.
6. Flexibility in the expression of intestinal hydrolases and transporters in response to a variety of dietary signals is mediated by both transcriptional adjustments, including the regulation of transcriptional factors on acetylated histones, and posttranscriptional adjustments.
7. Digestive performance of animals depends on both the genome of the host and the characteristics of the host's gastrointestinal microbiome.
8. The microbiome seems to be characterized by large beta diversity among hosts and by a common core metagenome and seems to differ among animals with different diets. As is the case with the host's traits, the microbiome is flexible, and its composition and function change with dietary shifts.

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DISCLOSURE STATEMENT

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