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Antibiotic Resistance and Population Structure in *Escherichia coli* from Free-Ranging African Yellow Baboons

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Two collections of *Escherichia coli* from human hosts and one from free-ranging African yellow baboons were examined for the ability to utilize various sugars (biotype) and for resistance to antibiotics. The frequency of antibiotic resistance in the *E. coli* flora of baboons that feed regularly in village garbage dumps was found to be no greater than that in baboons not associated with human habitation. The frequency of antibiotic resistance in *E. coli* isolated from baboons is similar to that in *E. coli* isolated from humans before the widespread use of antibiotics but significantly lower than that in recent isolates from humans. The biotype data indicate that the amount and distribution of genetic variation in the *E. coli* among free-ranging baboon troops are similar to those in isolates from humans. However, *E. coli* isolates from baboons are able to utilize a greater variety of sugars as their sole carbon source, possibly because of a greater variety of sugars in the baboon diet.

Population geneticists have generally ignored asexual or haploid organisms (16), and medical microbiologists have tended to concentrate on clinical, physiological, or molecular aspects of bacterial pathogens. Consequently, most of the many isolates of *Escherichia coli* have been obtained from humans (or from animals associated with humans) and often nonrandomly from ill or hospitalized individuals. However, *E. coli* is an interesting species for population genetic studies because of its ubiquity, genetic variability, linkage disequilibrium, large population size, ease of husbandry, short generation time, and the extensive body of knowledge concerning its molecular biology and physiology (11). Consequently, there has recently been a surge of interest in studies of nonpathogenic *E. coli* strains isolated from their natural habitat. This paper reports the results of a study of isolates of *E. coli* obtained from natural populations of the Tanzanian yellow baboon (*Papio cynocephalus*). Another study of antibiotic resistance among enteric bacteria sampled from free-ranging yellow baboons has recently been published (22).

Hartl and Dykhuizen (11) have recently reviewed the literature of *E. coli* population structure. Their conclusions may be summarized as follows.

(i) *E. coli* populations contain impressive amounts of genetic variation, even more than in eucaryotes. This genetic variation is detectable by several techniques, including serology (1, 3, 20, 21), electrophoresis (4, 5, 24, 26), biogrouping (6), and nucleic acid hybridization (9, 12).

(ii) Sympatric hosts tend to share some strains, although other strains are unique to individual hosts (5).

(iii) Some *E. coli* strains have a worldwide distribution, although others are much more restricted geographically (5, 23).

(iv) Chromosomal recombination among clones of *E. coli* is limited. This conclusion is evidenced by high linkage disequilibrium and by the presence of many distinct clones within individual hosts (26, 27).

(v) The intestinal flora of a host exhibits a great deal of variation, with many transient strains and a few resident and recurrent strains (4).

(vi) Antibiotic resistance is relatively common in modern *E. coli* isolates (7, 8, 10, 13, 14, 18) but quite rare in *E. coli* isolates collected before the routine use of antibiotics (7, 13). Antibiotic resistance determinants are often contained in plasmids, which play a major role in the adaptive evolution of bacteria and which may be involved in recombination much more frequently than chromosomal DNA (but see reference 17).

The subject of antibiotic resistance merits elaboration because of its relationship to the present study. Antibiotics are used extensively as medicines and in animal feed supplements, and the high frequency of antibiotic-resistant bacteria in many modern samples has been attributed to this increased environmental selection pressure (see reference 14). Moreover, since antibiotic resistance determinants are often contained in plasmids, the spread of resistance may result not only from selection among clones but also from the transfer of plasmids among clones and, in some cases, among species. Transfer of plasmids greatly increases the probability that pathogenic strains will acquire antibiotic resistance, which is a clinically important implication of bacterial population biology.

Although evidence for the role of environmental antibiotics in selecting for resistance among bacteria is widely accepted, the evidence is weakened by a shortage of baseline values of the frequency of resistance to which data from modern "selected" bacterial strains may be compared. The preantibiotic-era strains of *E. coli* used by Hughes and Datta (13) are the best control group so far reported, but it would be interesting to know the frequency of antibiotic resistance among bacteria from hosts which are not exposed to antibiotics from human sources.

We studied the variation in strains of *E. coli* from natural populations of baboons for two primary reasons: (i) to compare antibiotic resistances and population structures in *E. coli* from free-ranging higher primates with isolates from

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humans and (ii) to determine the patterns of within-host and between-host bacterial variation in free-ranging higher primates.

MATERIALS AND METHODS

Bacterial isolates. Three major collections of *E. coli* were examined. The first is called the baboon collection, and it consists of 394 isolates sampled in 1984 from yellow baboons living in Tanzania. (The sampling method is described below.) The baboons live in five separate troops, two of which (the human-associated [HA] baboons) feed almost daily at a village garbage dump and pilfer food from native huts.

The remaining three baboon troops are not human associated (NHA). These troops are located approximately 15 km from the HA troops and have nonoverlapping ranges. Although it is well known that adult male baboons can migrate between groups, it is unlikely that the HA and NHA groups exchange male members to any significant degree.

The second collection of bacteria (the ECOR strains), which consists of 72 strains isolated from a diversity of mammalian sources, mainly human, was compiled by Ochman and Selander (19) for the purpose of representing the range of genotypic variation occurring within *E. coli* as assayed by protein electrophoresis. Details on the sources of the strains and their electrophoretic type are found in reference 19 and in R. D. Miller and D. L. Hartl, Evolution, in press. With the exception of 12 strains isolated as pairs from six hosts, each of the strains was isolated from a separate host.

The third group of *E. coli* strains is called the Murray collection, and it represents 30 *E. coli* isolates among a diverse sample of *Enterobacteriaceae* collected by E. D. G. Murray between the years 1917 and 1954. Details concerning the Murray strains are provided by Hughes and Datta (13). Most of these strains were isolated from independent human hosts.

Sample collection and identification. The *E. coli* community present in free-ranging baboon hosts was sampled by inserting a sterile Culturette swab (Marion Scientific, Div. Marion Laboratories, Inc., Kansas City, Mo.) into freshly deposited feces of baboons under observation. These swabs contained transfer medium and maintained bacterial viability for 2 to 3 months. Date, baboon troop, and animal (if identified) were recorded, and care was taken to avoid collecting duplicate samples from any baboon during a sampling period. Back in the laboratory, swabs were streaked on minimal lactose agar plates (see below for recipes) and incubated at 37°C for 24 h. Single colonies were picked to minimal citrate and minimal lactose plates and incubated at 37°C for 24 h. Bacteria which grew on minimal lactose but failed to grow on minimal citrate (diagnostic characters of typical *E. coli*) were streaked on eosine-methylene blue-lactose and incubated at 37°C for 24 h. Single colonies were cultured and stored at −70°C. A genotypically diverse subsample of 25 baboon strains was tested with Enterotube II diagnostic tubes (Roche Diagnostics, Div. Hoffmann-La Roche Inc., Nutley, N.J.) to determine the adequacy of our diagnostic procedure. All isolates scored unambiguously as *E. coli*. Actually, our diagnostic procedure is conservative because occasional strains of *E. coli* are found to be lactose negative or citrate positive.

TABLE 1. Antibiotic resistance in four collections of bacteria

Strains	n^a	% of total isolates resistant to the following no. of antibiotics					
		0	1	2	3	4	5
Murray	30	93.3	6.7	0	0	0	0
ECOR	72	70.8	12.5	12.5	0	4.2	0
HA baboons	245	93.1	4.1	0	1.6	0.4	0.8
NHA baboons	149	89.3	2.7	4.7	3.4	0	0

[a] *n*, Number of isolates per collection.

TABLE 2. Distribution of *E. coli* strains resistant to five common antibiotics

Strains	n^a	% of isolates resistant to:				
		Chloramphenicol	Ampicillin	Streptomycin	Kanamycin	Tetracycline
Murray	30	0	3.3	3.3	0	0
ECOR	72	1.4	5.6	22.2	4.2	20.8
HA baboons	245	2.0	2.9	3.7	0.8	5.3
NHA baboons	149	0.7	6.0	6.7	8.1	0

[a] *n*, Number of isolates per collection.

Antibiotic resistance. All strains were tested for resistance to the following antibiotics (micrograms per milliliter): chloramphenicol, 12.5; ampicillin, 50; streptomycin, 50; kanamycin, 50; and tetracycline, 25. Survival of natural isolates after exposure to these concentrations often indicates plasmid-borne resistance (22). To facilitate the testing of 496 strains, a 60-prong inoculator was constructed by embedding the heads of aluminum nails in epoxy resin so that the exposed points formed a grid. The inoculator was flamed and used to mark gridpoints on a master plate containing Luria agar, and each gridpoint was inoculated with a separate strain and incubated at 37°C for 24 h. The aluminum inoculator was then used to make replica plates to test for antibiotic resistance. Replica plates were incubated at 37°C for 24 h. Strains were scored as plus or minus for growth in the presence of the antibiotic. Strains that exhibited weak or delayed growth on any antibiotic were streaked onto Luria plates containing the antibiotic to check for single-colony growth. In all cases, at most a few colonies appeared, implying that the weak growth resulted from new antibiotic resistance mutations. Thus, strains showing weak growth were scored as minus.

Carbon source utilization. The standard replica plating technique with sterile velvet was used to test all strains for ability to grow on the following sugars (grams per liter): rhamnose, 2; salicin, 1; dulcitol, 3; xylose, 3; sucrose, 0.5; sorbose, 1; raffinose, 2; and glucose, 0.5, used as a control. Test plates were incubated at 37°C for 48 h and scored as plus or minus for growth. Scoring for growth on sugars was somewhat more subjective than that for antibiotic resistance but was highly reproducible for strains tested repeatedly. To permit growth of amino acid-requiring or vitamin-requiring auxotrophs, the minimal medium containing each sugar was supplemented with the following (per liter): Casamino Acids, 1 g (Difco Laboratories, Detroit, Mich.); tryptophan, 0.05 mg; biotin, 0.122 mg; thiamine, 0.281 mg; pyridoxine hydrochloride, 0.103 mg; niacinamide, 0.061 mg; and *para*-aminobenzoic acid, 0.069 mg.

RESULTS

Antibiotic resistance. Tables 1 and 2 summarize the incidence of antibiotic resistance in 496 strains of *E. coli*. Of these, 25 (5.04%) of the strains were resistant to only one antibiotic, whereas 31 (6.25%) demonstrated multiple resist-

TABLE 3. Ability of four collections of *E. coli* strains to utilize sugars

Sugar	% Strains with positive growth[a]			
	ECOR (n = 72)	Murray (n = 30)	HA baboons (n = 245)	NHA baboons (n = 149)
Rhamnose	81.9	53.3	88.6	91.9
Salicin	0	3.3	13.1	40.9
Dulcitol	29.2	36.7	44.1	47.0
Xylose	95.8	63.3	99.6	99.3
Sucrose	12.5	10.0	7.8	24.8
Sorbose	44.4	46.7	62.4	78.5
Raffinose	38.9	3.3	69.0	65.8

[a] n, Number of isolates per collection. Strains manifesting growth after 48 h were scored positive.

ance. The most common resistance was to streptomycin (37 strains), followed by tetracycline (28 strains), ampicillin (21 strains), kanamycin (17 strains), and chloramphenicol (7 strains). Nonresistant strains greatly outnumbered resistant strains in all three collections and in all individual baboons from which seven or more strains were isolated. Perhaps surprisingly, baboons associated with humans (by feeding at a village dump) showed no higher frequency of antibiotic-resistant strains than did baboons from troops not associated with humans (6.9% versus 10.7% resistant, respectively; not statistically significant). Frequency of antibiotic resistance among the baboon isolates was similar to that in the Murray strains from the preantibiotic era (8.4% versus 6.7%, respectively), but both of these collections had significantly fewer resistant strains than the 29.2% found in the modern ECOR collection, which is biased toward isolates from humans in the United States and Sweden. The large number of strains resistant to streptomycin or tetracycline or both is largely responsible for the high frequency of antibiotic resistance in the ECOR collection. Since both the ECOR and Murray collections represent one isolate per host, multiple sampling from individual baboons could affect comparisons between the baboon collection and the other two collections. We eliminated this bias by subsampling the baboon strains in two ways: (i) random selection of one strain per sample and (ii) elimination of all repetitions of each biotype found within a particular sample. Neither of these subsamples was statistically different from the total baboon collection or resulted in different trends when compared with the ECOR and Murray collections with appropriate χ^2 tests.

Growth on sugars. Tables 3 through 6 summarize data from the biotyping experiments. Table 3 lists the percentage of strains from each collection which grew on each of the seven test sugars. Salicin and sucrose utilization were uncommon, but most strains could utilize xylose. On all sugars except sucrose, both the HA and NHA baboon collections had a higher frequency of strains with a positive score than did the ECOR or Murray collection. The percentage of strains with a positive score averaged over the seven sugars was highest in NHA baboons, followed by HA baboons, the ECOR collection, and the Murray collection. To estimate the variability of *E. coli* in each collection, we calculated the average number of sugars that strains in each collection could utilize (Table 4). All collections differed significantly from the others, and again the baboon strains could utilize more sugars than the ECOR or Murray strains. On average, isolates from NHA baboons were able to utilize more different carbon sources than isolates from HA baboons in nearby localities.

TABLE 4. Percentage of *E. coli* strains growing on various numbers of sugars

Strains	% Strains growing on the following no. of sugars							
	0	1	2	3	4	5	6	7
Murray	30	0	13	40	10	7	0	0
ECOR	0	11	19	35	25	8	1	0
HA baboons	0	6	9	21	35	22	4	4
NHA baboons	0	0	3	13	36	30	15	2

Biotyping. The terminology for identifying strains by metabolic capabilities (biogrouping) is unsettled. For the pur-

TABLE 5. Distribution of biotypes among four collections of *E. coli*

Biotype[a]								No. of strains isolated			
R	S	D	X	U	O	F		ECOR	Murray	HA baboons	NHA baboons
0	0	0	0	0	0	0			9		
0	0	0	1	0	0	0		8		14	
0	0	0	1	0	0	1				1	
0	0	0	1	0	1	1			1		
0	0	0	1	1	0	0					4
0	0	0	1	1	0	1		1			
0	0	0	1	1	1	0					1
0	0	0	1	1	1	1		2			
0	0	1	0	0	1	1		1			
0	0	1	1	0	0	0				11	
0	0	1	1	0	0	1		1			
0	0	1	1	0	1	0			4		
0	1	0	1	0	1	1				2	
0	1	1	1	0	1	0					2
0	1	1	1	0	1	1					5
1	0	0	1	0	0	0		14	4	10	
1	0	0	1	0	0	1		9		23	6
1	0	0	1	0	1	0		10	3	13	1
1	0	0	1	0	1	1		4		60	30
1	0	0	1	1	0	0		1			3
1	0	0	1	1	0	1				1	
1	0	0	1	1	1	0		1	1		10
1	0	0	1	1	1	1		1		2	1
1	0	1	0	0	0	0		1	1		
1	0	1	0	0	1	0			1		
1	0	1	0	0	1	1		1			
1	0	1	1	0	0	0		1	2	13	
1	0	1	1	0	0	1		3		13	3
1	0	1	1	0	1	0		7	2	3	5
1	0	1	1	0	1	1		3		43	14
1	0	1	1	1	0	1		1		2	1
1	0	1	1	1	1	0		1	1		5
1	0	1	1	1	1	1		1		3	4
1	1	0	0	0	1	0				1	1
1	1	0	1	0	0	0				1	8
1	1	0	1	0	0	1				1	2
1	1	0	1	0	1	0				4	2
1	1	0	1	0	1	1				3	7
1	1	0	1	1	1	0			1	1	2
1	1	0	1	1	1	1					1
1	1	1	1	0	0	0				1	
1	1	1	1	0	0	1					5
1	1	1	1	0	1	0				3	5
1	1	1	1	0	1	1				5	16
1	1	1	1	1	1	0				1	2
1	1	1	1	1	1	1				9	3

[a] Biotype designations: 1, growth; 0, no growth on rhamnose (R), salicin (S), dulcitol (D), xylose (X), sucrose (U), sorbose (O), and raffinose (F).

TABLE 6. Temporal distribution of biotypes of *E. coli* sampled from the HA baboon Blondie

Date	n^a	H^b	Biotype (no.)													
			A	B	C	D	E	F	G	H	I	J	K	L	M	N
14 April	11	1.9		2	2			3	3						1	
18 April	40	0.3				38			1						1	
20 April	46	2.3	1	1			2	5	26	1	1	1	4	3		1

[a] *n*, Number of strains isolated on each date.
[b] *H*, Shannon-Weiner diversity index.

poses of this paper, we shall use the term biotype to refer to the combination of scores from each of the seven sugars and the term resistotype for the five-score combination from the antibiotic tests. For purposes of comparison with the ECOR and Murray collections, it was convenient to combine the large HA and NHA baboon collections into one.

Examination of biotype characters revealed some interesting patterns. Of the total 46 biotypes in the three collections (ECOR, Murray, and baboon), 6 biotypes were found in all three. The baboon strains shared 7 biotypes with the Murray strains and shared 15 biotypes with the ECOR strains, whereas the ECOR and Murray collections had 7 biotypes in common.

Within the baboon collection (disregarding two troops with very low sample sizes), between 50 and 60% of the baboon *E. coli* biotypes in each troop were found only once. (This was also true of the ECOR and Murray collections, despite the difference in sampling protocol). Of the 29 biotypes found in more than one sample, 1 biotype was shared by all five baboon troops, 2 were shared by four troops, 8 were shared by three troops, 11 were shared by two troops, and 7 were unique to a particular troop. Of the 22 shared biotypes, 19 were found in both HA and NHA baboons.

Resistotypes also showed interesting patterns. Of the 15 resistotypes which contained at least one positive score, 6 were unique to a single sample. Of the remaining nine resistotypes, two were found in three baboon hosts, five were found in two baboon hosts, one was found in a single baboon host, and one was found in nine strains of the ECOR collection. Although some of the resistotypes were shared by the ECOR, Murray, and baboon strains (probably because of independent acquisitions), only one resistotype was shared by different baboon troops, and none was shared between HA and NHA baboons.

In four of the samples from baboons, several strains with different biotypes contained the same resistotype. Some of these biotypes differed by more than one sugar, increasing the likelihood that transfer of a resistance plasmid (rather than mutations of loci affecting biotype) had occurred.

Biotype diversity was quantified with the Shannon-Weiner diversity index (H) as $H = -\Sigma p_i \log_2 p_i$ where p_i is the frequency of biotype i in the collection. The rationale for choosing this particular diversity index is given by Lewontin (15). Mean biotype diversity of *E. coli* from individual baboons (excluding all animals from which fewer than seven strains were isolated) is 1.7. Approximately 40% of the diversity of the entire baboon collection is due to within-individual diversity, 39% is due to between-individual (within troop) diversity, and 21% is due to between-troop diversity.

Finally, one of the female HA baboons (called Blondie) was sampled three times in a 7-day period, allowing us to record temporal changes in *E. coli* fauna within an individual. Significant turnover of biotypes and a large variation in strain diversity were evident (Table 6).

DISCUSSION

Antibiotic resistance in *E. coli* strains from wild baboon hosts is less frequent than in strains from contemporary human hosts, but it is similar to levels found in *E. coli* collected in the preantibiotic era. This finding supports the hypothesis that widespread use of antibiotics among humans promotes the spread of resistance among bacteria. However, it should be emphasized that the level of antibiotic resistance found in the baboon isolates is not insignificant—about 8.5% of the strains were resistant to at least one of the antibiotics tested. Whether the maintenance of this level of resistance is because of the immigration of resistant bacteria from human populations, selection of correlated or pleiotropic effects of resistance plasmids, direct selection for resistance as a result of naturally occurring antibiotics, or some other force or combination of forces cannot be determined from our data. A relatively high basal frequency of antibiotic resistance, whatever the cause, would allow a population of bacteria to respond very quickly to antibiotics introduced into their environment.

In an analogous study of antibiotic resistance among coliform isolates from fecal samples of yellow baboons in the Amboseli National Park in Kenya, a significantly higher frequency of antibiotic resistance was found in a baboon troop that frequented a human refuse pit near a latrine area used by campers than was found in NHA animals (22). However, direct comparison with the present study is difficult because of differences in sampling methodology and data collection, nondiscrimination among species of coliform bacteria, and potentially important differences in exposure to antibiotics or human fecal material of the HA baboons in the study areas. Thus, the contradiction between the studies may be more apparent than real, but additional data will be necessary for resolution.

Despite differences in the methodologies used to determine population structure, our results confirm the findings of others with respect to the amount of variation in *E. coli* and its distribution in time and space. The large number of different biotypes among the baboon strains represents a wide variety of gene combinations, indicating great genetic diversity. Whittam et al. (26, 27) have concluded from the high levels of linkage disequilibrium and from other evidence found with electrophoretic data that chromosomal recombination in *E. coli* is so rare that reproduction in the species may be regarded as essentially clonal. In our study, the presence of multiple *E. coli* biotypes in individual baboons also suggests some degree of clonality. Moreover, many of the biotypes occurring within an individual baboon host cannot be explained by recombination among the other biotypes present in the same baboon.

Previous work with serotyping (25) and electrophoresis (4)

has shown considerable turnover in the genetic composition of bacterial populations within individual human hosts. Our data on the baboon Blondie showed very rapid and substantial turnover in biotype frequencies within a 6-day period. Much of this turnover could not be explained by recombination among strains already present in the flora (unless some strains were present in undetectable frequencies). These data therefore seem to support previous findings that invasion from extraintestinal sources is an important determinant of intestinal community diversity (reviewed in reference 11).

Relatively continuous environmental input combined with the overall genetic diversity of the *E. coli* population may explain the large variation in biotype diversity found among individual hosts and over time within a single host (Table 6). It is likely that this variation is not a reflection of the intrinsic characteristics of particular hosts but is instead due to a combination of the introduction of new bacteria, characteristics of the various strains of bacteria already colonizing the host, and chance extinctions of established strains. The importance of dietary input is supported by the work of Bettelheim et al. (2), who showed that humans eating sterile food harbor decreased numbers of *E. coli* strains.

Data on sharing of nonpathogenic bacterial strains among associated hosts are sparse. The most complete study of "normal" *E. coli* host distribution is that of Caugant et al. (5). In a study of five human families, they showed that an average of 11% of *E. coli* strains are shared by members of the same family, 5% are shared among families living in the same city, and only 2% are shared by people living in different states. The structure of baboon troops facilitates similar comparisons. Of the 37 biotypes found in the baboon collection, 8 (22%) were unique to a single individual, 7 (19%) were unique to a single troop, 3 (8%) were shared between troops within an HA category, and 19 (51%) were shared between troops in different HA categories. Although direct comparison of these two sets of data is not meaningful because of different sampling methods, both indicate that sharing of *E. coli* strains is not uncommon. In both studies, most of the strains which are shared within a small geographic area are also shared among larger geographic units. Whether widespread clones have adaptive characteristics which are responsible for their success is not presently known (5).

The number of sugars that *E. coli* strains are able to utilize can be interpreted as a measure of food-niche breadth. In this regard, the differences between the ECOR and Murray strains and the baboon strains are noteworthy. On the average, strains isolated from free-ranging baboons utilized a greater number of sugars than did strains isolated from human hosts or zoo animals (Table 4). In addition, many more of the ECOR and Murray strains lacked the ability to utilize particular sugars, especially salicin (Table 3). These results might be explained by the progressive loss of sugar utilization capabilities during prolonged storage. To assess this hypothesis with regard to the utilization of salicin and raffinose, we examined 21 strains of *E. coli* freshly isolated from patients with urinary tract infections at Washington University Medical Center. Only two strains (9.5%) could utilize salicin, and only three strains (14.3%) could utilize raffinose. These numbers are greater than those found in the Murray collection but are still substantially smaller than those found in isolates from NHA baboons (Table 3).

The finding of greater nutritional versatility among NHA baboons may imply that the diet of free-ranging baboons exerts a more varied set of selection pressures on the intestinal flora than does the human diet, and this hypothesis is supported by the reduced nutritional versatility observed among *E. coli* isolates from the HA baboons, which feed at the village garbage dump.

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