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INSIGHTS FROM MODEL SYSTEMS
Of Monkeys and Men: Vervets and the Genetics of Human-Like Behaviors

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A major goal of contemporary human genetics is the understanding of genetic and environmental interactions in the development of complex traits, with behavior being an especially difficult example. Although many other organisms already have contributed significantly to this study, the nonhuman primate provides a uniquely attractive model, since most species share >90% of their DNA with *Homo sapiens* and reflect one or another aspect of human behavior, even to the untrained eye. For example, although other mammals show equally complex social organization, a prolonged period of dependence and social learning is unique to primates. Patterns and rates of cortical and limbic brain development also are similar in humans and the Old World primates. These generalizations apply across many species of primates, but characteristic and stable patterns of social organization and individual behavior vary from species to species. Because of the idiosyncracies of different species of primates, not every human behavior of interest to geneticists will have a parallel in every nonhuman primate species. Our own experience with the African green, or vervet, monkey (*Cercopithecus aethiops*), which arose through a fortuitous combination of accident and intent, has revealed complex physiological and behavioral phenotypes—such as, hypertension, alcohol consumption, and anxiety, among others—that reflect features seen in human populations. As increasingly powerful tools for the study of the genetics of these traits in the vervet become available, this species promises novel insights into the roles of genes that influence behaviors shared by our two species.

The St. Kitts Vervet

Vervet monkeys were imported primarily from Senegambia to the Caribbean islands of St. Kitts, Nevis, and Barbados, during the last half of the seventeenth century (Labat 1722; McGuire 1974). Taxonomists have identified the St. Kitts monkey as being derived from *C. aethiops sabaeus* (Ashton and Zuckerman 1950, 1951; Poirier 1972), but it should now be considered a separate subspecies (*C. aethiops St. Kitts*). In both Africa and the Caribbean, the species is abundant, nonendangered, and a serious agricultural predator; it is among the least specialized of the Old World monkeys, being omnivorous and tolerant of climates and ecologies ranging from the swamps of Senegal to the savannahs of Kenya to the mountain slopes of Ethiopia (Struhsaker 1967*b*). The Caribbean population is under no predator pressure and carries none of the known African pathogenic viruses (McGuire 1974).

The basic troop structure is matrifocal and matrilineal, with multiple males and a juvenile:adult ratio of ~2 (Struhsaker 1967*a;* Gartlan and Brain 1968; McGuire 1974). Field studies reveal a readily defined dominant (alpha) male and a less easily recognized alpha female, which may or may not accept the alpha male as a consort. Young males leave the troop around the time of sexual maturity (5–6 years of age) and work their way into neighboring troops. Territory is well defined and is maintained by scent markings and active defense.

Breeding in the wild is seasonal, with summer being the peak birth season, after 6 mo of gestation. The female is sexually mature by ~3 years of age, and the successful rearing of her own infants requires social experience and learning within the group context. Mothers and aunts thus overtly teach the adolescent female how to hold and to carry a new infant, and, in naturalistic social groups, juvenile females baby-sit their younger sibs and relatives (McGuire 1974; Lancaster 1975; Fedigan 1982; Seyfarth and Cheney 1990).

Our work on this species began with the intent to model complex human behavioral disorders, within a framework of developmental biology and social organization. The standard tools of the neuroscientist have been employed, for example, in the study of brain injury and impulsive aggression (Steklis et al. 1975; Raleigh et al. 1979) and of Alzheimer-like dementia (Liberini et al. 1993; Pioro et al. 1993). We and others have used this

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primate extensively in neuroanatomical and neurobehavioral studies (Redmond 1987; Desjardins et al. 1995; Chaudhuri et al. 1996, 1997). An atlas has been created for the adult brain (Contreras et al. 1981), and there is extensive documentation of catecholaminergic and serotoninergic neurochemistry (Young and Ervin 1984; Redmond et al. 1986; Ellsworth et al. 1987; Raleigh et al. 1992; Sladek et al. 1995). As our breeding colony has grown, we have turned increasing attention to the study of complex traits that occur spontaneously in the population and for which a genetic basis might be plausible.

One reason complex diseases are complex is that the criteria for identification of normal and disease phenotypes are not obvious and, indeed, may be defined only by trial and error. Arbitrary diagnostic criteria standardize clinical communication but are unlikely to delineate genetically informative phenotypes. Even when genetic heterogeneity is acknowledged, it remains necessary to discriminate similar phenotypes, with reliable, often quantitative or statistically validated criteria. Case-control studies also suggest biological or behavioral markers that may cosegregate with the disorder, in multiplex kindreds. Although these phenotypes provide clues to the core disorder and also may decrease genetic heterogeneity, there is always the risk that a given phenotypic construct will be a so-called red herring that cannot be mapped or cloned. Nonetheless, we devote considerable resources to defining phenotypes, in the belief that this information will provide a more homogeneous basis for the mapping of specific vulnerability genes.

Elevated Diastolic Blood Pressure (BP): A Subtype of Hypertension?

Essential hypertension in the human population is clinically heterogeneous, with regard to both severity and presentation. Biochemical classifications, such as high-renin versus low-renin forms of hypertension and subgroups with differing autonomic reactivity, also have been proposed. The nature and severity of complications and the physiological responses to salt, stress, and antihypertensive drugs are also variable. At least some of these factors are likely to be influenced by independent genetic factors (Childs 1983; Hamet 1993).

In the vervet, spontaneously elevated BP occurs in 5%–15% of feral green monkeys (Kraft-Schreyer and Angelakos 1985; Martin et al. 1990). Breeding studies support the hypothesis that elevated pressure is highly heritable in this species, as it is in humans; results of segregation analysis have been most consistent with the presence of one or more major-locus (probably autosomal codominant) effects on diastolic BP (Kraft-Schreyer et al. 1987; Palmour and Ervin 1990). Body weight is a significant correlate of BP only during the juvenile period.

Hypertension in the vervet monkey reflects only a few aspects of the very heterogeneous disorder seen in humans but, nonetheless, provides a good example of the way in which quantitative, physiological, and clinical information can be combined, with respect to the derivation of phenotype. For example, some, but not all, standard antihypertensive medications acutely and selectively reduce BP in hypertensive vervets (Hamet et al. 1989; Martin et al. 1990). Hypertensive animals have low extracellular plasma volume, low to moderate renin levels, and minimal response to elevated dietary sodium (Kunes et al. 1992). BP is not elevated significantly by chronic social stress (R. Niaura and F. Ervin, unpublished data). Animals with elevated diastolic BP have increased mortality, at every age, and show left ventricular hypertrophy (LVH) as early as 3–4 years of age. This type of hypertension is stable for many years, then progresses into cardiac crisis with severe ischemia, arrhythmia, and a sustained drop in BP. In a few cases, this pathology has been documented by thallium scan and electrocardiography (F. Ervin and P. Hamet, unpublished data). Stroke is rare. Some vervet monkeys with long-standing severe hypertension exhibit secondary renal damage, but there is no evidence of primary renal hypertension.

In longitudinal family studies, elevated BP is a highly heritable trait in vervet monkeys; parental BP is a strong predictor of offspring BP ($P < .0001$). LVH and early cardiac damage cosegregate in these kindreds, whereas adrenergic responsivity segregates independently of either LVH or early cardiac damage. A small number of candidate loci have been excluded. This data set, which includes >100 full-sib pairs and >200 half-sib pairs, as well as a small number of three-generation kindreds with extensive routine BP measures, will be submitted to a full genome scan once the planned linkage map becomes available. Since it is highly likely that the vervet monkey has, at most, 2 or 3 dimensions of hypertension (rather than the 6–12 seen in the human population), genetic analysis is much more likely to successfully stratify this complex trait, in accordance with genetic (and ultimately mechanistic) bases.

Social and Abusive Alcohol Consumption

The eighteenth-century work *Journal of a Lady of Quality* (Andrews 1922) tells of slaves catching monkeys in St. Kitts with a concoction of rum and molasses in a coconut shell. Once the monkey had drunk to stupor, one only had to pick it up! Indeed, most vervet monkeys will drink some beverage alcohol, but, in the laboratory setting, only a few will drink in a fashion that would earn a psychiatric diagnosis (Ervin et al. 1990). To be precise, ~15% of ~1,000 animals screened from the feral population voluntarily con-

sumed >5 g ethanol/kg/d, and ~5% consumed >8 g ethanol/kg/d and repeatedly drank to coma. Between 10% and 15% drank little or no alcohol, and the rest drank small to moderate quantities but did not increase their consumption with continued exposure. This distribution is strikingly similar to that seen in the human population. Alcohol consumption (in grams/kilogram/day) is highly stable in adult vervets tested repeatedly over time and also occurs reliably in social groups. No behavioral training or dietary deprivation is required. This behavior contrasts sharply with that reported in most primates, which must be trained to drink and consume only modest quantities of alcohol (0.3–2.5 g ethanol/kg/d). It is also notable that vervet heavy drinkers will drink to the point of liver, heart, and gastric damage, providing a true model for human pathological alcohol consumption.

The behavioral phenotype of pathological alcohol consumption is clearly heterogenous in both monkeys and humans, and behavioral, pharmacological, and biochemical approaches all suggest at least two severe primate phenotypes, as well as a population profile very reminiscent of human drinking behavior. In the general monkey population, for example, most animals (so-called social drinkers) will drink more alcohol from noon to 4 p.m. than between 8 a.m. and noon, prefer their alcohol in a sweetened vehicle (as opposed to in water), and rarely will consume >30% of their fluid as alcohol (Palmour et al., in press). These moderate drinkers will consume 0.8–3.5 g ethanol/kg/d, with the large absolute quantity being the consequence of a fast metabolic rate. By contrast, heavy drinkers will drink more alcohol in the morning than in the afternoon, and, when access is restricted to a short period of the day, the proportion of fluid taken as alcohol (the alcohol:vehicle ratio) will increase sharply, to the extent that some animals can consume as much alcohol in 4 h as in 24 h. Heavy drinkers prefer alcohol in water (rather than in sweetened fluid), and, although the absolute quantity of alcohol consumed increases somewhat as alcohol dehydrogenase and aldehyde dehydrogenase are induced, the very high level of drinking, on first presentation, argues strongly against this behavior being viewed as a behavior reinforced by learning. Most heavy (and many moderate) drinkers also will drink local rum without any pairing of alcohol and sweet taste.

There are at least two types of heavy drinkers, which are not distinguished simply by the quantity of alcohol consumed. So-called binge drinkers, when given access to alcohol for a limited period of time, will consume most of their daily aliquot within 1 h of exposure and typically will not drink any water while alcohol is available. If alcohol is available continuously, they sometimes will drink repeatedly to intoxication or to coma, within a single 24-h period. In the social group, these animals will stand at the alcohol bottle and will drink continuously, blocking access for all other monkeys (if large enough and strong enough) (Ervin et al. 1990; Juarez et al. 1993). So-called steady drinkers also will increase their alcohol:vehicle ratio during limited access but rarely will drink to coma and typically will consume at least as much water as alcohol. Binge and steady drinkers also can be distinguished both pharmacologically and biochemically. For example, long-acting bromocriptine and certain other dopaminergic agents reduce alcohol consumption in the latter group but increase it in the former. Naltrexone is effective in heavy drinkers of either category but is ineffective in reducing the alcohol intake of social drinkers. Tryptophan also reduces alcohol consumption in both groups of heavy drinkers but is more effective in binge drinkers. Cerebrospinal fluid (CSF) homovanillic acid is significantly and inversely correlated with alcohol consumption, across the entire population, and is particularly low in steady heavy drinkers (Palmour et al. 1995). CSF 5-hydroxyindole acetic acid is very low in binge drinkers but is otherwise uncorrelated with alcohol consumption. Steady drinkers show an exaggerated lymphocyte adenylate cyclase response to agonist stimulation (Palmour et al. 1993) and have elevated levels of dopamine transporters in limbic striatum (Mash et al. 1996), whereas the lymphocytes of binge drinkers are abnormally unresponsive to agonist stimulation. Elevated dopamine transporters and exaggerated signal transduction are both reduced by chronic alcohol exposure and rebound with abstinence. It may not be irrelevant that these same biological markers characterize subpopulations of human alcoholics (Nagy et al. 1988; Virkkunen and Linnoila. 1993; Tiihonen et al. 1995; Dongier et al. 1996).

Determination of the heritability of these phenotypes is a complicated proposition. Not only are the two types of pathological drinking likely to involve different genetic substrata, but also the scoring of phenotype in offspring is confounded by the fact that alcohol consumption (in grams/kilogram/day) is higher in juveniles than in adults, perhaps in part because of the higher metabolic rates of youngsters. In addition, breeding animals can be studied only for brief periods each year, when females are neither pregnant nor nursing. Although sufficient numbers of second- and third-generation offspring are not yet available for a full segregation analysis, it is clear that the offspring of heavy-drinking fathers (of both phenotypes) will drink at least twice as much as the offspring of social drinkers and that, in turn, these offspring will drink nearly twice as much, on average, as the offspring of alcohol-avoiding monkeys ($P < .0001$). In this species, some females will drink just as avidly as males, but alcohol is never available in breeding groups: pregnant females with access to alcohol sometimes produce infants with features of fetal al-

cohol syndrome. Very preliminary data indicate that the offspring of binge drinkers show very high alcohol:vehicle consumption ratios and will drink at least 75% of a 24-h intake in 4 h of scheduled access. It also appears that the quantity and patterns of alcohol consumption can be predicted by baseline CSF levels of neurotransmitter metabolites, in young animals previously unexposed to beverage alcohol. Cluster analysis suggests four distinct combined phenotypes, on the basis of quantitative and qualitative aspects of alcohol consumption, as well as of pharmacological response and biochemical distinctions.

Those phenotypes that segregate in pseudo-Mendelian fashion suggest a number of candidate loci (e.g., genes affecting signal transduction or dopamine/serotonin neurotransmission). Although some of these candidates are already under investigation, our present knowledge of the multilayered nature of neurotransmitter regulation compels an eventual genome scan. Nearly 250 offspring (again, comprising many full-sib and half-sib pairs) of fathers defined with regard to alcohol consumption are already available for this investigation.

Anxious Behaviors

There is a sense in which each primate species can be characterized with a dominant personality type or temperament: *Macaca arctoides* is phlegmatic, and *Macaca mulatta* tends to be suspicious and aggressive. Within this framework, *C. aethiops* is an anxious species (Redmond 1987). Flight is much preferred to attack, most physical aggression is defensive, and common responses to startling stimuli include crouching, cowering, and hiding. This is, of course, an overgeneralization, since within the species there is a rich continuum of individual variability along a number of personality and temperamental dimensions. Individual vervet monkeys thus can be characterized as calm (so-called laid-back) or anxious (so-called uptight), on the basis of baseline social behavior and the response to standard behavioral challenges, such as those originally suggested by Suomi (1982) for the rhesus macaque (Higley and Suomi 1989). In the social group, laid-back monkeys explore more actively, are groomed more often, and compete more effectively for food, drink, and desired sitting and sleeping places (fig. 1). Uptight monkeys are more isolated, more frequently lose confrontations, and typically adopt crouched or cowering postures. In a single cage, anxious monkeys will often crouch on the floor of the cage, pace stereotypically, or exhibit bizarre postures, whereas calm monkeys typically sit quietly or attend to external stimuli.

We have exploited these individual differences in order to develop a pharmacological interaction model of panic disorder (Bradwejn et al. 1992). Anxious monkeys display frozen immobility, self-clasping, cowering, and huddling, in response to a challenge dose of cholecystokinin-tetrapeptide (CCK4), a naturally occurring peptide that induces panic attacks in patients with panic disorder (Bradwejn et al. 1991) and in some healthy volunteers (Bradwejn et al. 1990). This state typically is followed by 5–10 min of hypervigilance and wariness, which then evolves into a period of restlessness and motor activation, persisting for another 10–20 min. In calm monkeys (those that are indifferent to moderate behavioral challenge), CCK4 increases the frequency of and especially the duration of arousal behaviors but does not produce frozen immobility, even when given in a dose on an order of magnitude higher than that which engenders panic in anxious monkeys. Anxious monkeys are also more vulnerable to the anxiogenic and panicogenic effects of other classes of compounds (e.g., caffeine or yohimbine). Recent data suggest that anxious monkeys have lower baseline levels of endogenous CCK, an elevated endocrine response to stress, and an enhanced

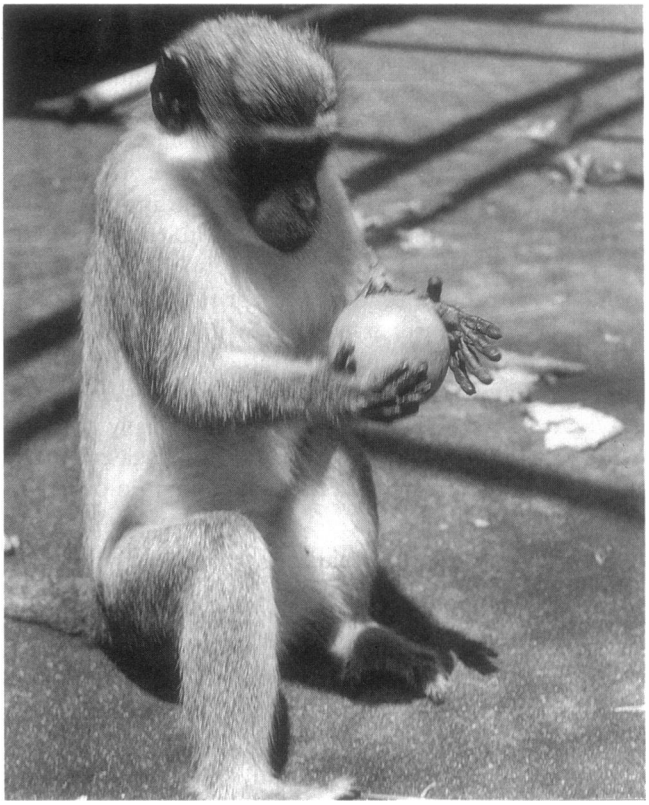

Figure 1 Juvenile vervet monkey displaying a behavior common to vervets and to humans. Exploratory behavior—for example, playing with a new toy—is characteristic of so-called calm individuals of this species. Some aspects of calmness or of anxiety are stable features of individual animals and correlate with parental phenotypes. Genetic analysis of temperament and of human-like behaviors, in the vervet monkey, should become easier as higher-resolution maps of vervet genomes and of other primate genomes become available.

receptor sensitivity to exogenous CCK4 (Merani et al., in press).

Do anxious parents have anxious offspring? This and other temperamental trait factors are the focus of a relatively new longitudinal study of infant development. All offspring born in the colony are scored by use of standardized behavioral checklists (drawn from both the human and the primate literature), in the natal cage, at the ages of ~3 wk, ~3 mo, and ~6 mo. After removal to the nursery, baseline biochemical and endocrinological samples are collected, and each infant is tested in a novel environment, at ~7 mo and again at ~12 mo. Social behavior is scored systematically for the juvenile peer groups, at ~18 mo and at ~24 mo. Although this study is still in the preliminary stages, it is clear that some dimensions of behavior are stable over time and that these stable behaviors are statistically correlated with parent behavior scores. Of most interest, however, is discordant sib behavior for stable traits, suggesting that segregating trait loci may be identified once an adequate genetic map is available.

One obvious question is whether there are correlations between alcohol consumption and either personality factors or social status, in the vervet population. Quite surprisingly, anxious monkeys typically avoid alcohol in both the social group setting and the individual testing cage. Conversely, prolonged alcohol exposure increases the anxious response in many animals. In the social situation, individual behavioral responses to alcohol consumption are varied: some animals become playful, some become morose, and some become abusive or combative. When drinking, most subordinate animals become quiet and isolated, rather than playful and outgoing. Heavy drinkers, whether of the binge or the steady phenotype, are rarely at the bottom of the social hierarchy, and, in fact, some rank at or near the top. Although it is tempting to speculate that these animals would score high on an extraversion vector, further study will be required to confirm or to negate that hypothesis and also to evaluate the preliminary suggestion that binge drinkers tend to elicit, rather than initiate, aggression.

Mapping Strategies and Methods

The vervet genetic map will be developed by use of microsatellite markers from the human genetic map. The extensive synteny between chromosomes of Old World monkeys and of humans (DeGrouchy 1987; Rogers et al. 1995; Perelygin et al. 1996) and the relatively limited divergence in DNA sequence between vervet and human genes suggest that a map of sufficient resolution can be constructed by use of the primer pairs commercially available for human mapping (see Rogers and Hixson 1997 [in this issue]). Several other groups have reported the use of human microsatellite-marker pairs, for primate mapping (DeGrouchy 1987; Rogers et al. 1995; Coote and Bruford 1996). In a small pilot project for this strategy, 10 of the 28 human primer pairs tested yielded adequate amplification for analysis by use of vervet DNA as a template. Our goal for the vervet genetic map is to place ~400 polymorphic markers on the vervet genome, with few gaps of >20 cM between markers.

The transfer of human markers to the vervet map will take place in several steps. More than 60 primer pairs that are known to reveal polymorphisms in other primates will be the first to be tested on vervets (Zhong et al. 1996). The next set of primer pairs tested will be those from Research Genetics, which includes >6,600 dinucleotide repeats, >2,300 tetranucleotide repeats, and 430 trinucleotide repeats in its MapPairs database of available primer pairs from the human map (Research Genetics 1997). If 20%–25% of these markers are informative in the vervet, the commercially available primer pairs should be adequate for the construction of a high-resolution map.

FISH with human genomic clones and chromosome-specific probes (chromosome painting) also will be used to confirm the relationship between the human and the vervet genetic maps. Human probes have been used on chromosomes from a number of primates, including the vervet, to investigate chromosome evolution and primate systematics (Ried et al. 1993; Stanyon et al. 1995; P. Eydoux and R. M. Palmour, unpublished data). A combination of chromosome painting and FISH should give us a detailed picture of the chromosomal rearrangements that separate vervet and human chromosomes and thus help to confirm the relationships between the respective genetic maps.

Why Map One More Genome?

The ultimate goal of the generation of a vervet map is to clone and to identify the genes that subserve complex traits such as hypertension, anxiety, or alcohol abuse. Our hypothesis is that the identification of these genes should lead to a better understanding of disease mechanisms and thus to a clearer rationale for the design of new therapeutics. The population structure, the availability of large numbers of animals, and the opportunity for the use of controlled breeding all work together to simplify the mapping process, while the vervet's close evolutionary ties to humans suggest that the genes discovered are likely to be important in the parallel human diseases. Even before specific genes will have been identified, it will be possible to discover, for example, if there is linkage to syntenic regions of the human and the vervet chromosomes. Since essentially the same maps will be used in both organisms, it will be possible to

compare directly the mapping data and to use each population for the confirmation of mapping results in the other. In addition to the type of manipulated gene-environment interaction studies described by Rogers and Hixson (1997), it also will be possible to study the interactions between specific genetic predispositions and psychosocial factors, in both naturalistic (social group) and experimental paradigms.

The study of complex diseases in general and of behavioral disorders in particular is plagued by a number of methodological problems. Among the most vexatious are the obvious clinical and genetic heterogeneity and the difficulty of defining a genetically informative phenotype (i.e., one that derives directly from the expression of a causative or a vulnerability gene). The uncontrolled convolution of environmental, social, and genetic influences in human populations further complicates the identification of phenotype.

Careful genetic analysis of a primate population derived from a relatively limited founder stock can overcome some of the difficulties of the study of complex diseases in humans, while avoiding the conceptual and practical difficulties of extrapolation from more distantly related experimental organisms. The vervet population of St. Kitts and Nevis offers an excellent and tractable model of certain aspects of human alcohol abuse, hypertension, and anxiety disorders. Development of a microsatellite mapping panel for the vervet will allow us to map and, potentially, to clone many of the genes involved in these complex diseases. This, in turn, will provide the opportunity to probe the pathophysiological correlates of these genes, in a fashion that would never be feasible in humans. Ultimately, however, a phenotype is only a phenotype if the gene can be found, and, more than any other desideratum, this motivates the present undertaking.

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