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DISEASE DIVERSITY AND HUMAN FERTILITY

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Abstract.—The existence of parasitic constraints on the evolution of life-history traits in free-living organisms has been demonstrated in several plant and animal species. However, the association between different diseases and human traits is virtually unknown. We conducted a comparative analysis on a global scale to test whether the diversity of human diseases, some of them responsible for high incidences of morbidity and mortality, were associated with host life-history characteristics. After controlling for direct confounding effects exerted by historical, spatial, economic, and population patterns and their interactions, our findings show that human fertility increases with the diversity and structure of disease types. Thus, disease control may not only lower the costs associated with morbidity, but could also contribute directly or indirectly to reductions in human population growth.

Key words.—Fertility, humans, infectious and parasitic diseases, life-history traits, multivariate analysis.

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A large body of recent literature elucidates different ways in which parasites may affect host fitness in plants (Alexander 1987; Thrall et al. 1993; Thompson 1995; Shykoff et al. 1996) and animals (Lively 1987; Hochberg et al. 1992; Forbes 1993; Lafferty 1993; Michalakis and Hochberg 1994; Møller 1997). Among the defences employed by hosts against their parasites (Combes 1995; Poulin 1998), one apparently subtle response is the adjustment of life-history traits (Stearns 1992). For instance, life-history theory predicts that when faced with virulent parasites, hosts should adjust their reproductive biology by increasing reproductive output and/or reducing age at maturity (Minchella 1985; Hochberg et al. 1992; Stearns 1992; McNamara and Houston 1996; Sorci et al. 1996; Reeson et al. 1998; Kris and Lively 1998; Brooke et al. 1998). Shifts in life-history parameters may be mediated by genetic change or via phenotypic plasticity (Minchella and LoVerde 1981; Pianka 1988), but very few studies have disentangled how different factors explain variability in life-history traits (Roff 1992).

Although parasitic and infectious diseases have had a major impact on human population demography around the world (Anderson and May 1991; Ewald 1994), few attempts have been made to relate how disease-causing agents have affected human biology and vice versa. To what extent have diseases influenced human biology? To what extent does fertility (i.e., the number of offspring born per female over her life span) influence the composition of the parasite and pathogen communities associated with disease? Answers to these questions require an understanding of the ecology and evolutionary biology of interactions between humans and their diseases (Stearns 1999). Most studies to date have only considered a small number of specific explanatory variables as determinants of human characteristics. These are often related to socioeconomic variables such as development, modernization, culture, family planning programs, and geographic and climatic descriptors (Jones 1990; Borgerhoff Mulder 1998). In contrast, biological factors, such as diseases considered in the present study (see also Clayton and Moore 1997; Poulin 1998), have been rarely assessed in studies on human life histories (but see Ewald 1994; Hrdy 1999).

Our objectives are to evaluate the importance of all major factors that have been traditionally identified by social scientists and demographers as possible causes of intercountry differences in disease-agent diversity (i.e., species richness and human life history) and to test whether the observed variation in human fertility might be sensitive to the diversity of parasitic and infectious disease agent species (hereafter called PIDS) and vice versa as predicted by life-history theory.

We employed a general linear model (GLM) to assess a possible direct effect of PIDS pressures on human fertility and vice versa across a large number of countries worldwide, when several potential confounding factors were assessed jointly and then controlled for in the analysis. Scant attention has been devoted to the effects of PIDS constraints on human life-history traits, and as such, GLM modeling might identify genuine relationships that more traditional socioeconomic analyses may mask. To our knowledge, this is the first time that a comparative analysis has attempted to detect a relationship between PIDS and human fertility while controlling for other potentially influential variables.

MATERIALS AND METHODS

Variables

We employed data from 150 different countries for which necessary population geographic and epidemiological information were available (see Guégan and Teriokhin 2000; Thomas et al. 2000).

Spatial patterns.—Because geographic and ecological factors might strongly influence variation in PIDS diversity and human life-history traits across countries, we considered five ecogeographic variables for each country: (1) total area of a given country (in square kilometers), because larger land masses may harbor higher PIDS diversity than smaller ones

(Brown 1995; Rosenzweig 1995); (2) mean latitude (in degrees and minutes, taken at the geographic center of each country), because higher species diversity is generally found in tropical areas compared to more northern ones (Brown 1995; Rosenzweig 1995); and (3) mean longitude (in degrees and minutes, measured as above), which accounts for PIDS dispersal along east-west gradients. These three environmental parameters were log-transformed to minimize the effects of nonnormality on statistics (Harvey 1982), and deviations from a normal distribution were tested using the Shapiro-Wilks test at the 0.05 level. Furthermore, we considered whether a country was located in the Northern (coded 0) or Southern Hemisphere (coded 1) and on mainland (coded 0) or an island (coded 1). All these data were compiled from the World Atlas version 2.1.0 (The Software Toolworks, Inc.).

Economic, social, and demographic patterns.— Because human PIDS diversity (and also human traits) might be associated with the level of urbanization or the amount of financial support for health care, we also compiled demographic and economic data for all 150 countries. Data for population geography were mostly obtained from the 1992 world population datasheet (Jones 1990). Seven demographic and/or economic parameters were retained for each country: (1) total population size, which represents the potential colonising pool for PIDS; (2) total population growth (per 1000 people), which gives an estimate of the reproductive capacity of a population; (3) population density (number of people per square kilometer), which is a proxy variable for urbanization; (4) total death rate (per 1000 inhabitants); (5) infant mortality rate (per 1000 live births in the first year of life); (6) life expectancy at birth; and (7) per capita gross national product (GNP in US dollars), as a proxy for resource levels. Total population size, population density, GNP, and infant mortality rate were log-transformed, whereas total population growth and total death rate were arcsine-transformed prior to analyses. To minimize problems associated with dimensionality and colinearity, we incorporated these seven source variables into a principal components analysis (see Statistical Analysis).

Religious patterns.—We considered the five main groups of religions: (1) Moslems; (2) Christians and Jews; (3) Hindus and Buddhists; (4) Shintoists, Confucianists, and related eastern religions; and (5) Animists (Jones 1990). We assigned a category to a country when at least 50% of its inhabitants belonged to one major religion.

Historical patterns.—To deal with the confounding effects of common genetic and cultural history on human traits and parasitism, we employed the human ethnic group phylogeny based on molecular data (Cavalli-Sforza et al. 1994). Unfortunately, it was impossible to directly use the entire phylogeny, mainly due to the existence of more or less well-recognized ethnological groups in our data. Thus, we considered only the eight largest divisions of ethnic groups: (1) Africans and Nilotics (except native peoples from the Maghreb); (2) Europeans (including peoples from the Middle East); (3) Indians; (4) Mongols, Japanese, and Koreans; (5) American Indians; (6) Papua New Guineans; (7) Melanesians; and (8) Chinese, Hmong, Khmers, Thais, Filipinos, Indonesians, and related tribes (Cavalli-Sforza et al. 1994). We used only countries for which at least 50% of inhabitants belonged to one major ethnological group, and we crossed the spatial, economic, social, and demographic patterns with this phylogenetic component. We omitted some countries (18 countries from a total set of 168) for which we were not able to attribute the population to a dominant tribe (e.g., Brazil, the former Soviet Union, and Republic of South Africa).

Disease patterns.— Disease occurrences (i.e., presence/absence) in the 150 countries were compiled from two different disease control sites, the Center for Disease Control and Prevention (CDC, Atlanta, GA, http://www.cdc.gov/) and the World Health Organization (WHO, Geneva, Switzerland, at http://www.who.int/). We collected data for a set of 16 categories of human parasitic and infectious diseases, each considered to have major detrimental effects on human health by the two institutions listed above. The presence of PIDS was determined on the basis of disease symptoms in humans, and not their presence in other animals or in the surrounding environment. When information to the parasite or pathogen species level was not available, we pooled data by disease category. Disease categories are as follows: typhoid, hepatitis A, hepatitis B, malaria, schistosomiasis, filariasis, meningococcosis, yellow fever, Dengue fever, cholera, African trypanosomiasis, dracunculiasis, Chagas disease, Lyme disease, cutaneous leishmaniasis, and visceral leishmaniasis. (We are aware that this is an incomplete list of human diseases, and further studies will be necessary to verify whether patterns found employing this list are retained in more complete lists). Based on this information, we calculated the total PIDS richness per country; PIDS richness in prokaryotes; and PIDS richness for protozoans, metazoans, insect vector-borne diseases, and water-borne diseases. These values are subject to some sources of error, e.g., some PIDS may have been recently introduced into countries and thus do not yet appear on available checklists or they may have been extinct for a number of years, but their effects on human populations still persist.

Human life-history patterns.—According to life-history theory and empirically demonstrated in numerous animal and plant species (see Introduction), some life-history traits might evolve through adaptation to selection pressures from PIDS. To examine a possible association between human life-history traits and disease pressures across countries, we investigated geographic variation in the occurrence of different PIDS and human fertility. Fertility is taken as the number of offspring born per woman, aged 15–44 years.

Statistical Analyses

The comparative analyses were performed by determining the relationship between disease pressures and human fertility when all other variables were controlled. We conducted these comparative analyses using GLMs for the 150 countries retained in the analysis.

To control for the effects of similarity due to common genetic and cultural ancestry, we used phylogenetic coding variables (see Harvey and Pagel 1991; Martins 1996). To deal with the problem of disentangling the interactive effects of development, cultural background, and socioeconomic patterns on fertility and disease measures, we employed a prin-

cipal components analysis (PCA; Jongman et al. 1995; Sheldon and Meffe 1995; Oberdorff et al. 1998). By reducing dimensionality and eliminating multicollinearity (James and McCulloch 1990), PCA forms linear, independent combinations of the original source variables. To account for possible effects of economic, social, and demographic patterns (see variables in the section Economic, social, and demographic patterns) in subsequent analyses, we retained three principal components (called PCDemog 1, PCDemog 2, PCDemog 3), all with eigenvalues greater than one. These three principal components were used in a GLM model to account for possible relationships between disease pressures or fertility estimates and sociological, economic, and demographic variables.

To test the hypothesis that diseases may be associated with fertility in humans or vice versa, we used GLM modeling with normal error structures (Venables and Ripley 1994). To assess possible directions of causation, we employed two models. First, we used the fertility estimates across countries as the response variable and the number of PIDS plus the different spatial, economic, social, demographic, and phylogenetic variables listed above as the potential explanatory variables. Second, we took the number of PIDS as the response variable of the reproductive output values and the different environmental, sociocultural, and economic independent factors. To select the two final models, we employed a backward elimination procedure from complete models (Zar 1996), with the tolerance option set at 0.05 (Wilkinson et al. 1992). Finally, the relationship between variation in human fertility and PIDS characteristics was examined by plotting relative values of fertility residuals, all other parameters listed above held constant, against the relative values of PIDS richness residuals, all other factors kept constant. Given that heteroscedasticity is common in cross-sectional data, we corrected for it by making variance-stabilizing transformations of the variables (see above). After final models, we plotted the residual values obtained from GLM models against predicted values to check for independence of residuals. The frequency distribution of residuals was also examined (Sokal and Rohlf 1994). Confidence intervals after multiple comparisons (the six different PIDS richness categories against fertility values) were computed after a sequential Bonferonni correction. For comparison i, if $p_i < \alpha/(1 + k - i)$ (where k is the total number of comparisons), then the correlation is statistically significant at $\alpha = 0.05$ (Peres-Neto 1999).

In a second step, we employed a Monte Carlo simulation procedure to evaluate the extent to which PIDS communities are structured across the 150 countries (Patterson and Atmar 1986; Guégan and Hugueny 1994). The global PIDS community is nested across countries if a disease-causing species found in a given country with n species has a high probability of being found in all countries with $n + 1$ species. Scores obtained from 20,000 randomly generated presence-absence matrices (each matrix having 150 countries × 16 possible PIDS were compared to the nestedness index (NI), which equals zero when the matrix is perfectly nested, and increases as the number of zeros (and therefore nonnestedness) rises. If it were found that communities were indeed nested, then a nested hierarchical design model (Zar 1996) would have to be employed to estimate the importance of a given block of species.

TABLE 1. Principal component characteristics for seven socioeconomic and demographic variables from the 150 countries analyzed. (a) The eigenvalue with the percentage explanation for each principal component and the cumulative percentage for the three components accounting for 90% of the total variability. (b) The principal component loading for the seven variables introduced into multivariate analyses. Loadings greater than 0.50 are in bold characters.

(a) Principal components	Eigenvalues		
	Total	Percentage of explanation	Cumulative percentage
PCDemog 1	3.304	47.202	47.202
PCDemog 2	1.922	27.460	74.663
PCDemog 3	1.045	14.932	89.594

(b) Variables	Principal components		
	PCDemog 1	PCDemog 2	PCDemog 3
GNP	**−0.883**	−0.105	−0.104
Total population	−0.028	**0.987**	−0.040
Total population growth	0.256	**0.945**	−0.024
Population density	−0.131	−0.021	**0.982**
Mean life expectancy	**−0.958**	−0.088	0.126
Total death rate	**0.795**	0.161	−0.183
Infant mortality rate	**0.944**	−0.099	−0.138

All statistical analyses were performed using Systat 8.0 (Wilkinson et al. 1992; Rawitch 1999) and SPSS vers. 8.0 (Chicago, IL) for PCs. The program for the Monte-Carlo simulations is available upon request.

RESULTS

Principal Component Analysis

The three principal components of the multivariate analysis performed on the country by socioeconomic and demographic variables explained nearly 90% of the overall variability across the 150 countries (Table 1). PCDemog 1 represents the environmental condition gradient with positive loadings for total death rate and infant mortality rate and negative loadings for GNP and mean life expectancy. PCDemog 2 distinguishes countries by population demography and is entirely uncoupled from mortality expressed by PCDemog 1. PCDemog 3 correlates positively with population density.

General Linear Model

Human fertility across the 150 countries was significantly correlated with total PIDS richness when all other influential environmental, demographic, and socioeconomic factors were controlled for (Table 2, Fig. 1). Spatial autocorrelation estimates were near zero (first order autocorrelation equal to 0.075). The standard partial beta regression coefficient relating disease to female fertility was remarkably large (Table 2; Std $\beta = 0.683$), demonstrating a strong association between the two variables. Another pattern emerging from this analysis (see Table 2) was the negative relationship between PCDemog 1 and fertility, which suggests that infant and adult mortality affect fertility through its effect on adult life span (see Thomas et al. 2000). The interactions diseases × area and diseases × ethnic group were also significant (see also

TABLE 2. Summary of general linear analysis of female fertility versus significant explanatory variables in which disease diversity is used as a potential explanatory variable across countries. Slope coefficients, standardized partial regression coefficients (Std β), degrees of freedom (df), *F*-ratios and associated probabilities (*P*) are given for each significant explanatory variable and interaction term. Results were obtained after a step-down backward elimination procedure with the tolerance option set at 0.05. The final model was highly significant ($R^2 = 0.977$, $n = 150$, df = 19, 130), $F = 313.799$, $P < 0.0001$).

Explanatory variables	Coefficient	Std β	df	*F*-ratio	*P*
Diseases	0.123	0.683	1	58.999	0.000
Area	−0.283	−0.060	1	119.352	0.000
Religion	·	·	4	7.421	0.004
Ethnic group	·	·	5	16.350	0.002
Longitude	−0.133	−0.046	1	30.497	0.000
PCDemog 1	−0.523	−0.122	1	68.906	0.000
Diseases × ethnic group	·	·	5	17.554	0.002
Diseases × area	−3.675	−2.498	1	43.682	0.000

analyses in Table 3). Moreover, the total number of PIDS per country was also associated with fertility when all other influential parameters were taken into account (Table 3, first order autocorrelation = 0.116). Again, the standard beta coefficient relating fertility to disease was very high (see Table 3; Std β = 0.187). The interactions fertility × latitude, fertility × PCDemog 1, fertility × ethnic group, and fertility × religion were also significant explanatory variables of PIDS richness (Table 3). After the sequential Bonferonni correction, only the relationships between total PIDS richness (Pearson's correlation $r^2 = 0.359$, $P = 0.006$), water-borne disease species richness ($r^2 = 0.375$, $P = 0.005$), and protozoan species richness ($r^2 = 0.328$, $P = 0.008$) and human fertility were significant (i.e., those involving prokaryotes, metazoans, and vector-borne diseases were nonsignificant).

Monte Carlo Simulations

Monte Carlo simulations indicated that diseases are distributed in a nested hierarchy across the countries employed in our study. Specifically, areas with progressively higher PIDS richness harbor diseases which, on average, are rarely found in countries with few PIDS (Fig. 2). Four diseases tend to depart from this nested subset pattern (Chagas disease, Lyme disease, cutaneous leishmaniasis, and to a lesser extent visceral leishmaniasis; Fig. 2), suggesting that these four outliers tend to be disproportionately found in species-poor countries. One reason may be the potential for biases in disease surveillance by the CDC and by WHO. For instance, it is possible that the recent description of Lyme disease has led to underestimates of its actual geographic incidence (i.e.,

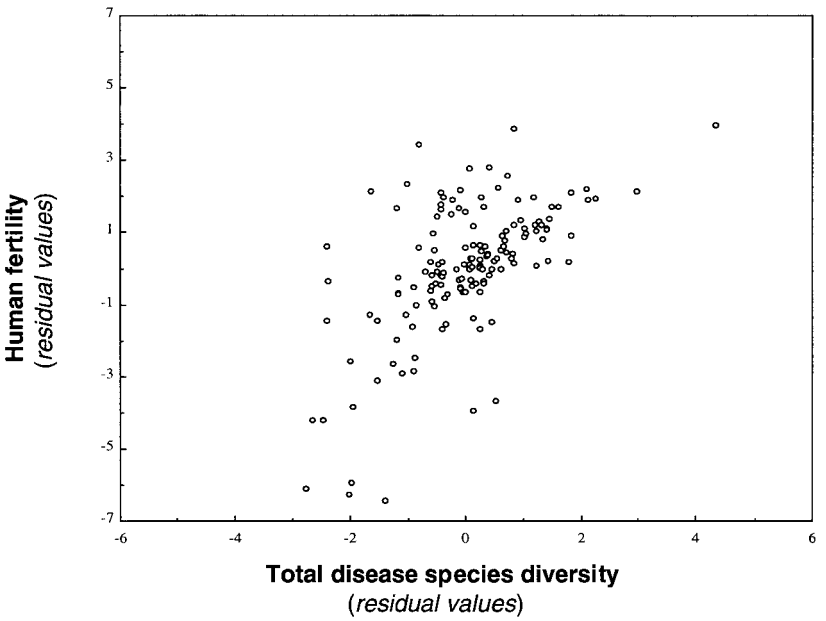

FIG. 1. Relationships between the residuals of mean human female fertility per country and total parasitic and infectious disease species richness ($r^2 = 0.359$, $P = 0.006$) when all other potential influential parameters were constant in the model for the 150 countries. Corresponding variations between residual and predicted values for both fertility and parasitic and infectious disease species diversity show no obvious sign of dependence of residuals, indicating that the multivariate analysis fits the data well ($n = 150$, $r^2 = 0.026$ and $r^2 < 0.001$, $P > 0.05$, respectively). Frequency histograms of both fertility and parasitic and infectious disease species diversity residuals indicate that most values are centred near zero ($n = 150$, mean = 0.105, SD = 0.001; $n = 150$, mean = 0.818, SD = 1.103, respectively).

TABLE 3. Summary of general linear analysis of human disease diversity versus significant explanatory variables in which human fertility is used as a potential explanatory variable across countries. Slope coefficients, standardized partial regression coefficients (Std β), degree of freedom (df), *F*-ratio and associated probability (*P*) are given for each significant explanatory variable and interaction term. Results were obtained after a step-down backward elimination procedure with the tolerance option set at 0.05 level. Final model was highly significant ($R^2 = 0.980$, $n = 150$, df = 18, 131), $F = 282.083$, $P < 0.0001$).

Explanatory variable	Coefficient	Std β	df	*F*-ratio	*P*
Fertility	3.053	0.187	1	90.563	0.000
Area	1.008	0.054	1	49.586	0.000
Hemisphere	0.557	0.070	1	12.716	0.001
Ethnic group	·	·	5	4.572	0.004
Fertility × latitude	−1.266	−0.087	1	66.392	0.000
Fertility × ethnic group	·	·	4	6.991	0.000
Fertility × religion	·	·	4	5.704	0.004
Fertility × PCDemog 1	0.641	0.049	1	16.733	0.000

it may not be monitored in many countries considered in our dataset). Alternatively, Lyme disease may be accurate, but it should soon spread to countries where we simulated its absence. In addition, the etiological agents of cholera and meningococcosis (i.e., *Vibrio cholerae* and *Neisseria meningitidis*, respectively) are likely to exist in every country sampled. The diseases they cause were probably not as widespread as their agents, because the latter rarely come in contact with human hosts.

Simulated results were highly significant: NI = 674, $P < 0.00001$ for the 16 diseases; NI = 323, $P < 0.00001$ for the 12 diseases with Chagas, Lyme, cutaneous and visceral Leishmaniasis withdrawn; and NI = 230, $P < 0.00001$ for the water-borne diseases. This overall nonrandom distribution of disease is an indication of interactions between the different PIDS (Fig. 2). Thus, PIDS occurrence across countries cannot be treated as statistically independent. We accounted for this problem using nested design models (Zar 1996), and found that the significance of the association between fertility (response variable) and PIDS composition (independent variable) across countries was explained to a considerable extent by a set of cooccurring diseases: Dengue fever, filariasis, schistosomiasis, cholera, meningococcosis, and yellow fever ($R^2 = 0.511$, *F*-ratio = 6.818, $P < 0.001$), all but one being water-born diseases. Meningococcosis is spread by aerosol during contacts between infected and uninfected individuals.

DISCUSSION

Classical demographic and social scientific theories explain variability in human life-history traits by cultural, geographic, and socioeconomic variables (Jones 1990; Borgerhoff Mulder 1998; Warren 1999). Because a wide array of factors may contribute to the actual variation in human traits, GLM models are a powerful tool to disentangle the respective

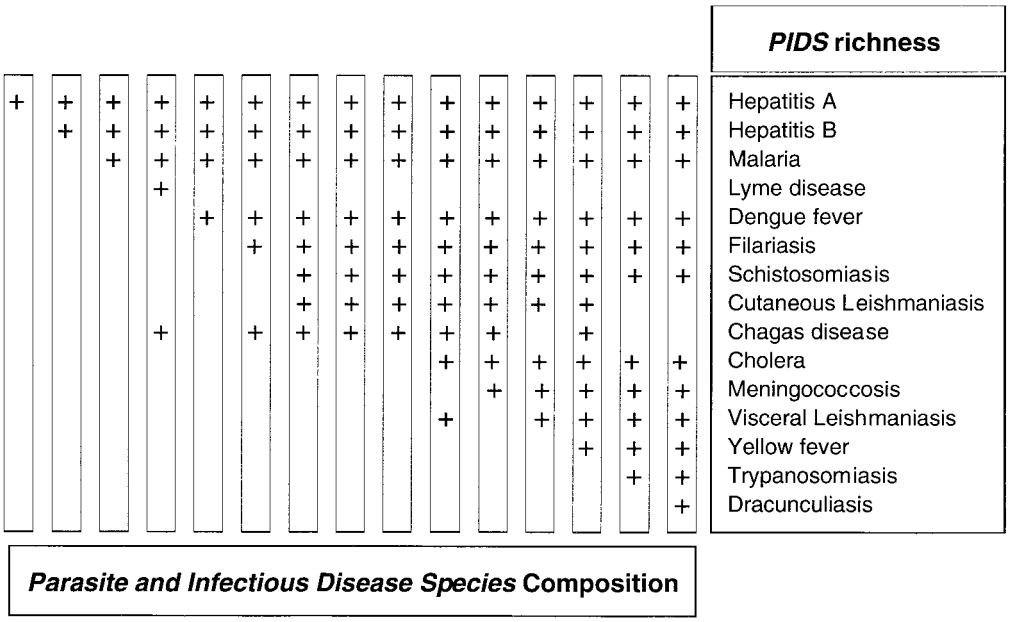

FIG. 2. Simulated distributions after 20,000 permutations of the 15 parasitic and infectious diseases (typhoid withdrawn) across the 150 countries, illustrating a nested species subset pattern. Each rectangle represents a different country, and countries are arranged from least (left) to most (right) species rich. Three diseases (Chagas disease, Lyme disease, and cutaneous leishmaniasis), and to a lesser extent visceral leishmaniasis, do not closely match the perfect nested design.

effects of socioeconomic, spatial, cultural, and biological characteristics, while controlling for potential confounding variables. Although we found that many nonbiological factors are indeed significantly associated with human fertility across countries, when they are correctly controlled for, a significant relationship emerges between parasitic and infectious disease species diversity and human fertility. This finding is in agreement with a recent suggestion made by Short (1999) that many human attributes are reflections of parasite fauna (see also Ashford 2000).

Although data are currently insufficient to assess any causal mechanism between parasitism and human fertility, our results can be compared and contrasted with two previous predictions. First, Connell (1971) has argued that diseases should be most virulent in the tropics, and Møller (1998) has suggested that tropical diseases should exert higher selective pressures on their hosts than temperate species. Together with our analysis, this indicates a positive association between parasite virulence and host fertility. Mathematical models in which virulence evolves in response to host reproduction support this prediction (Hochberg et al. 2000), whereas those where fertility is optimized as a function of virulence sometimes support and other times refute (Hochberg et al. 1992; van Baalen 1998; Koella 2000) the prediction. No models exist to test the argument that there is no causation; that is, both virulence and fertility vary as a function of extrinsic variables.

A second prediction is that women in countries with high diversities of virulent parasites either reach reproductive maturity earlier than women in countries with low disease species diversity (Hochberg et al. 1992) or produce more total children over the same or shorter reproductive life span (Minchella 1985). Either of these responses have genetically and/or culturally transmitted components, and either may be expressed constituitively and/or induced by direct or indirect contact with disease agents. Unfortunately, we currently cannot distinguish the possible influences of these various mechanisms.

If human fertility is indeed labile over short time periods to the composition of PIDS communities, then we predict that the most striking effects should be observed when a small number of influential diseases (e.g., those associated with water and/or keystone disease species) are eradicated. In contrast, we cautiously suggest that countries experiencing invasions by disease-causing agents should consider taking appropriate control measures to avoid their demography being significantly shifted to higher fertilities. If there is a direct or indirect causal relationship between disease control and human fertility, then disease eradication may not only reduce the costs of disease morbidity, but may also, paradoxically, curb the growth of the human population. Female education has been found by many demographers to be the single most predictive variable for fertility, but we suggest that a series of proximate, intermediate, and ultimate determinants comprising also biological factors must operate at different spatial scales to affect fertility variation.

In conclusion, although a wide array of historic and/or socioeconomic variables contribute to explaining variability in human fertility worldwide, population biology in the guise of disease species diversity and community composition contributes independently and importantly to explaining this variability. Further analyses that include other kinds of pathogens (e.g., viruses) are necessary to confirm our findings.

Acknowledgments

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