noglobulins varied enormously and that passively transferred serum from some infected animals but not others provides protection, one might conclude that immunoglobulins as a whole were ineffective. We induced RF in rats by using Freund's complete adjuvant (FCA) and by using lipopolysaccharide (LPS). The serum of such rats agglutinated IgG-coated *T. lewisi* at reciprocal titers even higher than those observed with serum from noninfected lactating rats [32 to 64 (*3*) and 4 to 8 (*4*), respectively]. However, when challenged with *T. lewisi*, such FCA- and LPS-treated rats did not show the enhanced resistance to *T. lewisi* shown by lactating rats. Therefore, the FCA- and LPS-induced RF's are not protective although the lactation- and infection-induced RF are protective (2).

Nemazee and Sato (*5*) subsequently but independently developed a similar yet broader concept of a positive role for RF. They studied the interactions of monoclonal antibodies and their antigens and observed that some monoclonal RF's interacted only with idiotype-anti-idiotype matrices and that others interacted with idiotype-antigen matrices. They found specificity for a subclass of IgG in their monoclonal RF's which has also been observed in (a polyclonal) RF-containing antiserum (*6*). Nemazee and Sato referred to these RF's as "enhancing antibodies." Since this term already has a very different meaning (*7*), we prefer the term "amplifying antibody."

Davis and colleagues (*8–11*) have found evidence that RF provides protection from the immune complex–induced tissue damage associated with the autoimmune disease systemic lupus erythematosus (SLE). For example, (i) RF can inhibit complement fixation by immune complexes (*8*); (ii) when RF is injected intraperitoneally into rats together with immune complexes or aggregated IgG, RF enhances their clearance and decreases the observed serum complement depletion (*9*); (iii) there is a positive correlation between the age of a patient at the onset of SLE and the appearance of RF, and a negative correlation between these and kidney disease associated with immune complex deposition (*10*); and (iv) RF directly inhibits complement-mediated immune complex deposition on human kidney glomeruli in vitro (*11*). Indeed, RF has recently been found to protect against immune complex–induced kidney damage in schistosomiasis (*12*).

More direct experimentation will be required to establish the relation between RF and *T. cruzi* infection. However, we have confirmed and extended the finding by Krampitz and Disco (*13*) that lactating mice are more resistant than nonlactating mice to *T. cruzi* (*3*). Whereas 67 percent of (20 of 30) lactating S/W mice survived challenge with *T. cruzi*, only 18 percent (6 of 34) of nonlactating mice survived. The differences in the patterns of parasitemia in our *T. cruzi*-infected lactating and nonlactating mice (*3*) were similar to those in our lactating and nonlactating *T. lewisi*-infected rats (*4*); initially the parasitemias increased at the same rate, but the parasitemias in the lactating mice had a lower peak and a shorter patent period. In *T. lewisi* infections this was due to the lactation-induced RF (*2, 4*). The time at which the parasitemias in the two groups of *T. cruzi*-infected mice deviate is correlated with the time at which IgG first appears on circulating parasites (*14*). We transferred protection from lactating to nonlactating mice by injecting 0.3 ml of serum from the former into the latter: nine out of ten mice survived the challenge that was fatal to the ten control mice that received 0.3 ml of serum from nonlactating donors. We suspect, but have not proved, that the transferred protective factor is an RF.

Although not pointed out by Cabral, we did omit a procedural detail in our report (*2*) which allowed a reasonable alternative explanation of our results. Immunoconglutinins are similar to RF's except that they are directed against bound, activated complement components (ACC) (*15*). Since we inactivated both of the sera containing the sensitizing IgG and the RF by heating, thus eliminating ACC participation, an immunoconglutinin could not have been responsible for our results.

Although we certainly agree with Cabral that better drugs and a better means of combating the pathology are major goals for research on Chagas' disease, we also believe that new approaches to controlling the disease may be derived from studies not directly associated with *T. cruzi*.

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Mass Extinctions in the Fossil Record

Raup and Sepkoski (*1*) statistically examine the marine fossil record to test the proposition that apparent "mass extinctions" might simply represent stochastic variation in an underlying extinction process. They perform a linear regression on the disappearance rates of marine families over the Phanerozoic and conclude that (i) overall extinction rates of families appear to have declined over time and (ii) four events (late Ordovician, Permian, Triassic, and Cretaceous, and possibly a fifth in the late Devonian) are distinct outliers, not adequately explained by the regression model. They postulate that these disappearances are likely to represent phenomena qualitatively different from the typical extinction processes.

Within the limitations of poor preservation and taxonomic uncertainty, Raup and Sepkoski's conclusion that familial extinction rates have declined over evolutionary history is convincing (Fig. 1A). The second conclusion, that four "mass extinctions" are statistically discernible from the regression appears to depend on the mechanisms assumed for the "background" extinction process. Raup and Sepkoski do not state a mechanistic model of extinction. Their regression technique is based on the assumption that the number of extinctions in each time period is independent of both the number of families present and extinction rates in adjacent periods and, for the statistical tests, that the deviations are normally distributed random variables. Raup and Sepkoski note that the independence assumptions are unlikely to be strictly met by their data set, although they do not analyze the consequences.

Deriving the expected distribution of "random" extinction rates depends heavily upon the extinction process envisioned. However, it is not clear what kind of extinction process would cause extinction rates to be normally distributed. The normal assumption cannot be strictly valid, as the confidence intervals include a substantial proportion (roughly 10 percent) of negative extinction rates. Empirically, the distribution of points around the regression line (not shown) departs significantly from a normal curve ($G^2 = 51.4$; d.f. = 3; $P \ll .001$) (*2*) and is quite asymmetric, suggesting that testing for outliers against a model of a symmetric distribution is likely to lead to error.

It would be theoretically and empirically more satisfying to assume that the errors in extinction rates are approximately log-normally distributed. Theoretically, it corresponds to a model of "random extinction" in which a family's survival probability over a long period of time is the product of the survival probabilities over a large number of independent random events. The logarithms of long-term survival rates, and thus extinction rates, are then sums of logarithms of random variables, and by the central limit theorem are expected to be roughly normally distributed.

Figure 1A shows the data from Raup and Sepkoski's regression replotted on a log scale (*3*). The new estimated regression relationship

$$\ln (\text{extinction rate}) = 0.0018\ (\text{million years}) + 0.70$$

is similar to that calculated by Raup and Sepkoski, but the location of confidence intervals differs substantially. The dashed lines represent estimates of three standard deviations about the mean in extinction rates, between which approximately 99 percent of the data points would be expected to fall. As in Raup and Sepkoski's analysis, the decline in extinction rates over time is significant ($P < .001$). The regression r^2 increases from 0.07 in the normal model to 0.16 in the log-normal model. None of the 76 points falls more than three standard deviations from the regression line. Four (the reputed "outliers") fall between two and three standard deviations above the line, more than the 1.5 points expected, but hardly enough to establish a significant group of outliers.

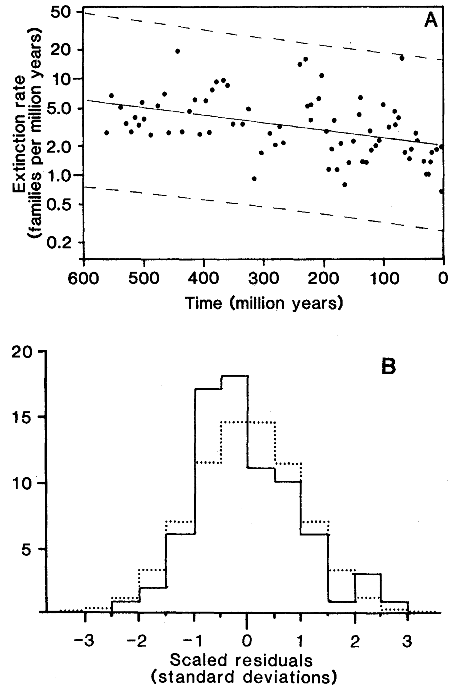

Fig. 1. (A) The rates of disappearance of marine families. The solid line is the regression of the log of the extinction rate against time. Dashed lines are three standard deviations of the observations from the mean. (B) The residuals of (A) divided by the estimated standard deviations of the extinction rates (solid line) and the expected distribution under the log-normal regression model.

Analysis of the residuals also gives no indication of outliers. The distribution of the deviations from the regression line is symmetrical, shows no major gaps, and appears normally distributed. Figure 1B shows the deviations divided by their estimated standard deviations under the log-normal model. It forms a reasonable approximation to the expected distribution [*t* distribution, 74 degrees of freedom] shown by the dotted line ($G^2 = 11.1$, d.f. = 9, $.2 < P < .3$) (*4*). The points Raup and Sepkoski believe are outliers (the highest four points) do not convincingly depart from the rest of the distribution.

Raup and Sepkoski have raised an important issue and have identified and collected the kind of information needed to resolve it. Despite limitations in the data and inherent problems in applying regression techniques to time series, it may prove possible to analyze rigorously the proposition that events identified as "mass extinctions" stand out from the distribution of other extinction episodes in the fossil record. Raup and Sepkoski's estimates of instantaneous extinction rates may be quite conservative, as the effects of possibly sudden events are averaged over millions of years. If the Cretaceous, or other major extinctions, actually occurred over months or years, rather than millions of years, as has been argued (*5*), the observed extinction rates would certainly rise above "background" by any reasonable statistical test. In this particular data set, however, the rates of extinction appear to be distributed roughly log-normally and, if so interpreted, show no obvious outliers. More precise dating or a better understanding of the process of "random" extinction might well allow more sensitive tests, but the available data on extinction rates do not seem to offer any compelling evidence for the occurrence of statistically distinguishable "mass extinctions."

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Quinn's (*1*) thoughtful reanalysis of Raup and Sepkoski's data on extinction rates of fossil marine families (*2*) is most welcome, both because it corroborates the conclusion that global extinction rates have declined over geologic time and because it permits us to reexamine the statistical basis for recognizing mass extinctions. Quinn presents two major criticisms of Raup and Sepkoski's statistical analysis. The first is an empirical criticism, noting that Raup and Sepkoski used statistical tests which assume normality on data that were clearly not normally distributed. The second is a more important, theoretical criticism, noting that Raup and Sepkoski did not have an explicit, rational model relating extinction processes to their data and that this adversely affected their choice of statistical tests.

The reasons why Raup and Sepkoski used linear regression analysis in the manner they did can be seen by examining the structure of their analysis. They began by accepting the traditional paleontologic view that there are two basic kinds of extinction in the fossil record (*3*): background extinction, which may vary with time, and mass extinction, which is of greater magnitude than background extinction. Because these two populations could not be identified a priori in the data (in part because of sampling noise), Raup and Sepkoski initially analyzed the entire untransformed data set of 76 measured extinction rates, using least-squares regression analysis. This resulted in a rather poor fit with residual extinction rates strongly skewed, as noted by Quinn. Raup and Sepkoski, however, interpreted the large positive outliers as reflecting the admixed population of mass extinctions. They then eliminated these outliers (using one-sided tests rather than two-sided as employed by Quinn) and reanalyzed the rarefied sample of 67 points. The second linear regression [figure 1 in (*2*)] fit the data better and left residuals that were much more symmetrically distributed—comparable, in fact, to Quinn's [figure 1B in (*1*)].

This procedure was rather ad hoc but, on empirical grounds, seems no less valid than Quinn's. Thus, the real question is whether Raup and Sepkoski's use of an implicit linear model and untransformed data was justifiable. We believe that Quinn is correct in arguing that this was not justified, but we do not agree with his alternative.

Quinn argues that "errors" in extinction rates are more likely to be log-normally than normally distributed, reasoning that "a family's survival probability over a long period of time is the product of the survival probabilities over a large number of independent random events." We can formalize this qualitative argument by considering that if there are n independent hazards over each unit of time and each is fatal with a probability equal to λ/n, then

$$\text{Prob(survival to time } t) = [1 - (\lambda/n)]^{tn} \approx e^{-\lambda t} \qquad (1)$$

Thus, the survival times should be approximately exponentially distributed, which is characteristic of a Poisson process, not of log-normally distributed rates.

The Poisson process is, of course, a common theoretical model for the occurrence of rare events (*4*). Indeed, it is a mathematical conclusion (akin to the central limit theorem) that, when dealing with aggregates of individual independent processes, the aggregate will behave like a (possibly inhomogeneous) Poisson process, even if the individual processes do not (*5*). Therefore, we suggest considering the number of extinctions X recorded in a time interval of duration d to be approximately Poisson distributed with parameter $\theta = \lambda d$, where λ represents the intensity of the extinction process over the interval as in Eq. 1. The probability that k extinctions will occur in d then is

$$\text{Prob}(X = k) = e^{-\theta}\theta^{k}/k! \quad \text{for } k = 0, 1, 2, \ldots .$$

Given this probability distribution, the appropriate transformation for analyzing actual data is the square-root transformation (*6*). $\sqrt{X}$ should be approximately normally distributed with a mean $\sqrt{\lambda d}$ and a constant variance. Furthermore, the square root of the extinction rate $(= X/d)$ also should be approximately normally distributed with a mean $\sqrt{\lambda}$ and a variance proportional to $1/d$.

A square-root transformation of Raup and Sepkoski's data provides statistical results intermediate between those of the untransformed data and the log-transformed data. A regression analysis (*7*) with all 76 data points results in the function

$$\sqrt{\text{rate}} = 1.52 + 0.0012 \text{ (million years)}$$

The residuals are less skewed than those generated by Raup and Sepkoski's initial analysis but more so than those in Quinn's analysis (*8, 9*). Four points (the Ashgillian, Maestrichtian, Dzhulfian, and Guadalupian) are possible outliers, with standardized residuals of sizes 3.36, 3.00, 2.87, and 2.65 (*10*). The first two of these residuals reach Quinn's threshold of three standard deviations for outliers.

Still, stringent significance tests for outliers, such as attempted by Raup and Sepkoski, are probably not fully appropriate in this case because, due to the considerable noise in the data, even the smallest of the possible outliers exceeds the fitted regression value by a substantial factor (that is, a multiple of four). Therefore, we can conclude only that the strong positive skewness that persists after the square-root transformation reflects a tendency for extinctions to cluster in a non-Poisson way. But since the extreme residuals do not stand out as a discrete cluster (as shown also by Quinn), it is entirely possible that the initial assumption of Raup and Sepkoski, that background extinction and mass extinction constitute two discrete populations, may not be correct. Instead, there may be a continuum of processes linking the traditionally observed mass extinctions with background events. Indeed, the occurrence of at least nine "minor" mass extinctions among the points interpreted as background extinction [see reference 11 in (*2*)] supports this speculation. However, as Quinn correctly concludes, higher resolution data and more precise extinction models are still needed before any such speculations can be tested definitively.

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7. A weighted least-squares form of regression analysis was used, in which the durations of the 76 time intervals were employed as weights. This weighting gives the longer intervals more weight in the analysis, and it is theoretically appropriate under the Poisson hypothesis.
8. Values for r^2 are not given as they are not properly comparable among the various analyses with untransformed, log-transformed, and square-root transformed data. The variance of the dependent variable must be computed on the same scale for such comparisons to be meaningful.
9. We agree with Quinn that the use of a logarithmic transformation still cannot be ruled out on empirical grounds, but, lacking a theoretical case for it, we feel that it is inappropriate for judging the existence and significance of outliers. The effect of choosing a transformation on entirely empirical grounds is to force extreme observations into line with the rest, masking the effect of interest.
10. If we assume that 0.01 is the probability that a point will lie more than 2.65 estimated standard errors from the regression line, as would be the case for a t-distribution with 74 degrees of freedom, then the binomial probability that at least 4 of 76 points will be that far is only 0.007.

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