Molecular Drive

While, in general, we have few quibbles with the substance of Roger Lewin's clear description of the genetic system of molecular drive (Research News, 5 Nov., p. 552), several comments in his article merit further discussion.

In our two papers (*1*) in which we detailed the factual basis and theoretical implications of molecular drive, we defined it as a process of fixing a mutation within multigene and nongenic families in a population, as a consequence of DNA turnover. Considerations of rates of turnover indicate that individuals of a sexual population would change in unison with respect to the changing composition of a family. At the heart of molecular drive is the widespread phenomenon of concerted evolution. Although the reality of this phenomenon is incontestable, we cannot accept the definitive statement of Lewin's, drawing in particular on remarks made by Alec Jeffreys about the human globin cluster and Alu family, "that it is not a universal phenomenon."

Concerted evolution is occurring in the globin cluster; indeed this phenomenon was first defined as such in this cluster due to the homogenization of pairs of α and γ genes, and their flanking sequences, by unequal exchange or gene conversion. In reviewing such events in the globin cluster, Jeffreys has written, "clearly, concerted evolution is not a rare phenomenon, and seems to occur between even distantly related genes and between active genes and pseudogenes" (*2*). In the case of very large families, such as Alu, detailed consideration needs to be given to the rates of homogenization relative to the mutation rate. A 10 percent level of sequence variation between 10 cloned Alu repeats from the human genome (*3*) reflects the constraints on homogenization imposed by the presence of 500,000 copies finely dispersed over 46 chromosomes. Despite these constraints the very low levels of homology revealed by hybridization between human and mouse Alu families reflects a much greater divergence between species than within species. Furthermore, the human Alu family has been homogenized throughout by an imperfect dimer, while the mouse Alu family consists only of monomers (*3*). Turnover is occurring in the Alu family, albeit slowly. We are not aware of families, whether tandem or interspersed, genic or nongenic, that are immune from such processes. The evolutionary progress of each family under molecular drive and the subsequent interaction with natural selection are expected to be very different (*1*).

The importance of molecular drive as a genetic system can only be assessed by consideration of the way in which the genetic and phenotypic cohesion of a population is maintained. An instructive example is provided by the phenomenon of hybrid dysgenesis in *Drosophila*. In this example, the molecular process is one of transposition, one of the three mechanisms underlying molecular drive. A slow rate of transposition of P elements would lead to a genetic situation in which there would be little variation in the number of P's in each individual at any one time during the initial accumulation of the element. The small variance in P number would not lead to dysgenesis within the population, as is observed. A large difference, however, in P number between a P population and a non-P population does lead to dysgenesis. Precisely the same low variance pattern of fixation would result from the slow rates of unequal exchange or gene conversion involving the homogenization of existing families for one variant or another.

Given this cohesive system of genetics, which contrasts remarkably with the classical population genetics of single-copy genes, we allowed ourselves some freedom in speculating on its involvement in the origin of the ontogenetic and reproductive differences between species. So far as we are aware, there are few experimental tests of the genetic mechanisms that are thought to underlie species differences. We do not disagree with the conventional viewpoint that such differences might be consequential when natural selection and genetic drift are working within Mendelian populations. Nevertheless, such external processes of fixation are inadequate in explaining species differences in multiple-copy families, that is, the phenomenon of concerted evolution. The evolution of such families and their manifold phenotypic effects can be partly explained by the genetics of molecular drive, which is precisely based on internal molecular mechanisms of turnover. Consequently, we are perplexed that Ford Doolittle and Robert Selander consider our speculation on the evolutionary biology of molecular drive to be unhelpful. We consider that all evolutionary biology may be, in essence, a manifestation of molecular events, and the artificial separation of molecular and evolutionary biology is itself unhelpful.

Part of the problem seems to stem from a mistaken supposition that turnover is only observed in nongenic families whose biological effects have yet to be ascertained. Concerted evolution is an extensively documented observation in many multigene families. The biological effects and evolutionary significance of changes in these families cannot be seriously challenged. It could well be that even the species differences in behavior emphasized by John Maynard-Smith are under multigene control. A population could undergo a long-term collective transformation in behavior under the aegis of the genetic system of molecular drive.

We do not consider molecular drive to be a catch-all for all genomic rearrangements and exchanges. If some rearrangements, for example, inversions, deletions, or duplications, turn out to be one-off events, then they are analogous to most point mutations that rely for their evolutionary progress on selection and drift. They do not contribute to the process of molecular drive.

From what we now understand of the activities of unequal exchange, gene conversion, and transposition in so many different families, the evolutionary differences between species must be considered a complex outcome of three processes of fixation—adaptive, accidental, and cohesively driven. Despite the seeming pitfalls in trying to promote a new perspective, we see no reason to be unenthusiastic about the implications of molecular drive.

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2. A. Jeffreys, in *Genome Evolution*, G. A. Dover and R. B. Flavell, Eds. (Academic Press, New York, 1982), pp. 157–176.
3. W. R. Jelinek and C. W. Schmid, *Ann. Rev. Biochem.* **51**, 813 (1982).

Oncogenes

In his letter of 15 October (p. 214), John W. Littlefield points out that the cell line NIH 3T3 is an imperfect recipient for experiments designed to capture "oncogenes" by gene transfer from tumor cell genomic DNA. I agree. The

genes so isolated by the laboratories of Weinberg, Wigler, Cooper, and others (Research News, 14 May, p. 724) are striking in their similarity to viral oncogenes and to each other. If we were to accept the notion that these are the genes mutated by environmental agents, then the target size for the environmental mutagenic component of carcinogenesis would be very small indeed, about 1/100,000 of the cell genome.

I suspect rather that these oncogenes represent familial genes for susceptibility to cancer, rather than genes whose somatic mutated alleles are the result of environmental insult. If so, then the interesting question becomes, Which are the genes that the environment acts on? Here I think one can more fully elaborate Littlefield's point. Those genes are likely to be the only ones that cannot be obtained in the NIH 3T3 transfection assay, because NIH 3T3 cells are already transformed with regard to the phenotypes they control. Therefore I predict that they will be found as the set, probably a large set, of genes recoverable when NIH 3T3 is used as a donor, normal precrisis cells are used as recipients, and the selective assay is based on some of the differences between the two cells, such as colony-forming ability, growth in low serum, or infinite lifetime.

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Empirical Research in Economics

I write in response to Wassily Leontief's letter of 9 July (p. 104) criticizing academic economics.

The most powerful ideas are the most sweeping ones, and so they are necessarily the most abstract and require statement in precise and manipulable terms. It is not surprising that the official journal of the American Economic Association would seek out theoretical articles. They become the basis for empirical research or they are fundamental because they might challenge such research. For example, the hottest theory extant in economics is that of rational expectations, which challenges standard macroeconometric research.

Leontief focuses misleadingly on one journal. The explosion in economic study is reflected in an explosion in the number of journals, many of which specialize in empirical work.

There is no doubt that theory is more glamorous than fact-grubbing and that the more elegant the theoretical presentation, the higher up stands the economist in the pecking order. Leontief argues that this distorts the allocation of resources between theory and empiricism in the profession. Whether the workings of a "free market" are interfered with by an academic elite or whether a "free market" would still not allow for externalities from an over-abundance of theory are perhaps key questions. My own feeling is that mathematical generalizations are the most powerful generalizations, and I do look up to those who demonstrate these skills in the pursuit of interesting (widely applicable) theories.

Leontief should cast more doubt on empirical research. Perhaps the problems may lie in the arbitrary assumptions that have to be made because of inadequate data. And Leontief has rightfully been in the forefront of those rebuking the U.S. government for budgetary cuts that affect the data base. But stochastic disturbances, the infinite variability of human behavior, make the results of empirical research relevant to a limited time-space context and invariably of little help in forecasting.

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Appeal from the Soviet Union

Well aware of the permanent attention given by your journal to the problems of international solidarity of scientists, I ask you to publish my letter. Only the really wretched and inhuman conditions in which I have been forced to exist for a long time are compelling me to write it in search of help.

In January 1981, I was fired from my position as a junior research member of the Institute of Philosophy of the U.S.S.R. Academy of Sciences, and since then I have not been able to find any other employment. The reasons for the dismissal had nothing to do with my professional performance. Being a specialist in science studies, I have published since 1974 about 40 papers in the fields of history, sociology, and philosophy of science; but, being a Jew, I committed an unforgivable crime when I began to exchange letters and offprints with foreign fellow students on my own 3 years ago, as my superiors decided that these communications clearly revealed my secret intention to find a job abroad. So I was discharged as soon as possible under the false pretext that my unpublished monograph *Aspects of Theory of Science* did not correspond with the aims of the Institute of Philosophy. As a rumor that I was going to leave this country quickly spread through the circle of my colleagues, I was virtually placed on a black list, with my professional career completely ruined. For a year I have been trying to appeal to the Academy authorities, but all my attempts have been in vain. I meanwhile received a formal invitation to come to Caltech as a visiting professor, but I was not even able, being a person without an official status, to apply for an exit visa. At last, after 15 months had passed, I was compelled to ask for permission to emigrate from the U.S.S.R. On 23 July, I was refused on the absurd pretext that I had no sound motives for emigration.

I never intended to make my case public, but now I have no other choice. I am quite certain that I shall never be permitted to continue my professional life in the U.S.S.R. and, because of my health, I cannot even earn my living working as a yardkeeper. Any day I can be legally expelled from Moscow on the grounds of my so-called parasitic mode of life. I know the power of the public opinion of scientists, and now I am appealing to the international scientific community and setting all my hopes on its understanding and assistance.

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Not Normal Littermates

In the caption of the photo accompanying the article "Brain receptors for appetite discovered" (Research News, 29 Oct., p. 460), the mice shown with an obese mutant animal are incorrectly identified as normal littermates of the obese.

The nonobese mice are, in fact, the mutants Himalayan and piebald spotting and illustrate size difference only. The obese (*ob*) gene is maintained on C57BL stock at the Jackson Laboratory, and the normal littermate is therefore also black.

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Erratum. In the report "Color vision is altered during the suppression phase of binocular rivalry" by Earl L. Smith III *et al.* (19 Nov., p. 802), four entries in Table 1 (p. 803) were incorrect. The dominance scores at 460 nanometers should be 4.37* for both subjects E.S. and D.L., and the dominance scores at 640 nm should be 4.37* for E.S. and 4.64* for D.L.