fabrication processes become concomitantly more complicated, yields are decreased by defects in the cells.

The now traditional means of dealing with low yields in DRAMs is to incorporate extra rows or columns of so-called redundant memory cells. If a defective cell is found in one of the normal rows or columns, it can be disconnected and replaced by a redundant cell. IBM has stayed with this approach in its 4-Mb DRAM. The chip includes 96,000 redundant memory cells. It is interesting that the state-of-the-art DRAM at the start of the 1980s had a total of 64,000 cells.

As memory size grows, redundancy becomes less practical, according to the NTT way of thinking. The alternative is the use of error-checking and error-correcting circuitry. Such circuitry can also test for and fix errors due to electric charge generated in memory cells when ionizing alpha particles pass through the chip, a significant problem when the storage capacitors are small. The downside of error-correcting circuitry is that it slows down the operation of the memory.

Three years ago, NTT researchers introduced a then experimental 1-Mb DRAM with such circuitry but there was a substantial 20-nanosecond "access penalty," enough to prevent its use in commercial memory chips. This year the NTT group redesigned the error-correcting circuitry and reduced the access penalty to 5 nanoseconds. The space occupied by the circuitry is about 10% of the total chip area.

To address a third problem, both NTT and IBM departed from the industry-standard 5-volt power supply for their DRAMs, lowering the operating voltage to 3.3 volts. The lower voltage is necessary to reduce the electric fields in the tiny structures making up the transistors and other devices on the chip, thereby preventing the degradation of device performance by high-field effects.

A crucial specification of any memory device is the access time or time to retrieve a bit of information from a memory cell. IBM's 4-Mb chip is quite fast for a DRAM with an access time of 65 nanoseconds, which compares favorably with the 80-nanosecond access time in the company's most advanced 1-Mb memory. Although perhaps not so meaningful from a computer point of view, some idea of the speed comes from the realization that this corresponds to retrieving in less than a quarter of a second the 400 pages of double-spaced typewritten text that the chip can store. The NTT 16-Mb chip operates with a quite respectable 80-nanosecond access time. The fastest DRAM at the conference was a 1-Mb chip with a 35-nanosecond access time from the Hitachi Central Research Laboratory in Tokyo. ■ **ARTHUR L. ROBINSON**

The Surprising Genetics of Bottlenecked Flies

The great majority of theoretical models have led researchers to expect a genetic impoverishment when a population is founded from a small number of individuals; new experimental results appear to confound these expectations

"You have to be crazy to do this sort of thing," says Edwin Bryant of the University of Houston. "It is incredibly laborious." Bryant is referring to a series of quantitative genetics experiments that he and his colleagues Steven McCommas and Lisa Combs have just reported, in which they measured the effects of passing houseflies through what geneticists call population bottlenecks. "I didn't think anyone would ever do this experimentally, because it is so tedious," observes Charles Goodnight, a theoretician at the University of Illinois, "but I'm delighted with the results."

"I think what happened with theoretical analyses of bottlenecks is what often happens with mathematical representations of biology."

The genetic effect that Bryant and his colleagues saw in populations of flies that had bred from 1, 4, and 16 male-female pairs in three separate experiments was an increase in variance, not a decrease as most mathematical models of bottlenecks would imply. In other words, there was more variability in some of the flies' physical characteristics—such as wing size and shape—in the post-bottleneck population than in the ancestral population, whereas the general expectation is that there would have been less. "Yes, at first sight it seems counterintuitive," comments Brian Charlesworth, a theoretician at the University of Chicago. "The results are clearly important, but I'm not yet fully sure what the implications are."

Goodnight is delighted with the Houston researchers' data because shortly after they were published he reported a theoretical model that essentially points in the same direction. "We've come to similar conclusions, but from completely different directions," says Goodnight, "and that's got to be encouraging."

Charlesworth's uncertainty about the implications of these new results is not because bottlenecks occupy an obscure backwater of quantitative genetics research. They don't. Since the 1950s bottlenecks have been part of an intense debate among geneticists, a debate that touches both on the mechanisms of the origin of new species and on conservation biology. An understanding of bottlenecks is therefore undoubtedly important. Charlesworth's uncertainty derives from the immense complexity of genetic processes that apparently operate through bottlenecks, a complexity that he and other theoreticians have attempted to address with several elegant but competing mathematical models.

"This uncertainty is not going to be resolved quickly," says Alan Templeton, a geneticist at Washington University who has played a key role in recent exchanges in the long debate. "But Bryant's results are important because we are finally getting the kind of information we need in order to evaluate these alternative models."

The potential genetic consequence of a bottleneck can be envisaged by thinking about one highly variable gene locus in some kind of hypothetical population. "Suppose you have 200 alleles at that locus within the population," explains Bryant, "and then you take two individuals, a male and a female, and begin a new population from them. The maximum number of alleles at that locus that can get through the bottleneck is four, which at first sight is a tremendous loss of variability."

The loss is tremendous, of course, but most of the 200 different alleles will be extremely rare in the original population and will therefore contribute only minimally to variance of the trait—such as wing dimensions in Bryant's experiments—influenced by this gene locus. "So, although a drop from 200 alleles to four is a sharp decrease in absolute genetic variability at the locus, it is a much smaller reduction in

genetic variance expressed in the population. But it *is* a loss, and this is what our experimental results are now challenging."

In one of the classic papers of genetics, Ernst Mayr, of Harvard University, in 1954 invoked the apparently inevitable decline of genetic variance after a bottleneck as a potential catalyst to the formation of new species. Known as the founder effect, Mayr's formulation assumed a catastrophic loss of variance. First Sewall Wright and later Richard Lewontin, also of Harvard, and Masatoshi Nei, of the University of Texas, pointed out that the reduction would be less than might at first be imagined, along the lines of Bryant's explanation above.

In a 1980 paper Russell Lande, of the University of Chicago, emphasized the simple formulation of $1/2N$ for the loss of variance, where N is the number of individuals in the founder population. So, he argued, in a population founded from a single male and a single female, the lowest level to which variance would fall would be $1 - 0.25$, or 75% of the value in the original population. He pointed out that the new population must reproduce prolifically if this level of variance was to be retained, because each subsequent generation is a potential bottleneck where the $1/2N$ formulation would apply.

In the experiment that Bryant and his colleagues conducted with houseflies, the bottleneck sizes were 1, 4 and 16 mating pairs. According to Lande's formulation, these would have produced post-bottleneck populations with genetic variances of 75, 94, and 98% of the original population, respectively. "Clearly, our results are discordant with these expectations," note the Houston team. In fact, in measuring heritability and variability of traits such as wing width, wing length, head width, separation between the eyes, and limb dimensions, Bryant and his colleagues recorded an increase in variance for most of these traits in the post-bottleneck populations, sometimes dramatically so. The post-bottleneck populations had reached about 2000 individuals before the Houston team painstakingly measured the suite of eight traits on a total of 3000 flies.

Not every trait came through the bottlenecks in the same way with respect to variance, but the overall pattern was clear: variance within the post-bottleneck populations was boosted, but particularly so in bottlenecks of intermediate size (4 and 16 pairs). This, says Bryant, is what requires explanation.

Initially the Houston team thought their results might simply be wrong, so discordant were they with theoretical predictions. But Bryant began to search the literature and came across a paper from 1952, by Alan Robertson, entitled "The effects of inbreeding on the variation due to recessive genes." This was a theoretical treatment that suggested that in small, inbreeding populations, rare recessive alleles might by the effect of chance sampling become much more common, and therefore increase the variance for that particular trait expressed in the population.

"Bryant's results are important because we are finally getting the kind of information we need in order to evaluate these alternative models."

Here, it seemed, were Bryant's results foreshadowed. "Yes, that's true," says Charlesworth, "but since that time people haven't paid much attention to what Robertson said." Robertson had obviously hit upon something interesting, but the subsequent literature on the subject all but ignored it. Why?

"I think the reason has to do with the inevitably limited power of models when faced with the great complexity of the real world," suggests Bryant. The core of the problem here is that, as every geneticist knows, there are several different brands of variance. The simplest occurs when two different gene loci affect a trait in a simple, additive manner: gene A acting in concert with gene B might produce a wing twice the length than if gene A were acting alone, for instance. The result of interactions of this sort is known as additive variance, and is readily tractable to mathematical modeling.

The world, however, is not that simple and many, perhaps most, gene interactions are nonadditive. The most straightforward example is dominance, where one allele at a locus simply masks the effect of a second allele. Another example is where a heterozygote at a locus is superior in some way to either of the homozygotes, an effect that is termed overdominance. Both dominance and overdominance involve interactions between genes at a single locus, and the variance they engender is nonadditive. A third category is nonadditive interaction of various sorts between different loci, which generates what is termed epistatic variance. These three forms of nonadditive variance are progressively more complex in the biological world and progressively more challenging to the theoretician who wishes to model them mathematically.

"I think what happened with theoretical analyses of bottlenecks is what often happens with mathematical representations of biology," suggests Bryant. "When you first start modeling a process you necessarily simplify it so you can at least begin to tackle what is inevitably a very complex system. In this case people said 'we can handle additive variance, but nonadditive variance is more complicated, and epistasis is a nightmare.' And, as often happens, you go from a simplifying process that gives you an approximate answer to thinking that you've got *the* answer." The result was that the theoretical focus was aimed principally at additive variance while the less tractable phenomena were pushed aside, if not completely out of sight. "Yes," agrees Charlesworth, "it is easier to think about genes with purely additive effects."

The irony is that if variance in the real world were limited exclusively to the mathematically tractable additive effects, then bottlenecks would indeed decrease it, just as Lande's formula says they would. The theoretical emphasis of additive variance therefore built up a certain expectation of the effect of bottlenecks, even though the researchers were by no means ignorant of the more complicated phenomena. And yet, according to the Houston team's experimental data and Goodnight's recent theoretical results, it may be that nonadditive variance is more important in the genetic outcome of founder events than are additive effects.

When Bryant and his colleagues were faced with the unexpected enhancement of post-bottleneck variance they had to look for models that might match their overall pattern, in which enhancement was greatest for bottlenecks of intermediate size. A straightforward dominance model, of the sort that Robertson had devised in 1952, did produce certain features that matched the experimental results with the flies, including an initial decrease in the viability of the population. But increase in variance in the dominance model was greatest in the smallest bottleneck population. "I think dominance is involved in this to a great extent," says Bryant, "but I don't think it is the whole story."

A model of overdominance also failed to match the post-bottleneck pattern, giving greatest enhancement of variance at largest bottleneck sizes. The mathematical model that came closest to the experimental results was, says Bryant, a representation of epistasis, in which a series of gene loci had multiplicative effects among them. "Some combination of dominance and multiplicative epistasis therefore seems to fit our data best," observes Bryant, "but of course that doesn't prove our interpretation is correct."

Charlesworth, for instance, is skeptical, particularly about the Houston group's mathematical representation of epistasis. "It is not clear that in their experiments they are dealing with anything other than dominance effects," he comments. Nevertheless, he does add that "Bryant's experiments are important, because they remind one that it is not always reasonable to assume that characters have strictly additive genetic control."

The kinds of traits that are governed by nonadditive genetic effects are important in nature, because as a group they often influence fitness: for instance, these traits affect body size and reproductive characteristics. The fate of such genes as a population squeezes through a bottleneck is therefore important to the fate of the newly founded population, whether in terms of the origin of a new species or the continued viability of the existing one.

"The dogma of bottleneck theory has always assumed that the newly founded population is somehow at risk, because of the predicted lower genetic variance," says Bryant. The Houston team's results clearly challenge this dogma. Bryant admits, however, that at least some of the increased variance stems from the greater representation of harmful recessive alleles that in the ancestral population exerted minimal overall influence. "It's true that the average fitness might be lowered," he says, "but as the variance is increased this gives you—to put it teleologically—a greater opportunity for selection to act on new and fitter genetic combinations."

Goodnight agrees. "Our two papers show that perhaps there is something else we should be looking for in founder events. We have an increase in variance and possibly a shift in what different alleles are doing, a shift in the value of existing alleles." Templeton is enthusiastic about this emerging picture, because it is closely allied to what he and, independently, Hampton Carson of the University of Hawaii have proposed.

It is early days yet and the impact of the results from Bryant's group and from Goodnight remain to be assessed, but ideas on speciation and on conservation biology are certain to be questioned. Meanwhile, as Templeton says, "We need to know a good deal more about what exactly is going on, in terms of what kinds of alleles you have, what kinds of interactions exist, and how exactly they are modified through a bottleneck." ■

ROGER LEWIN

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Bottlenecked Cheetahs

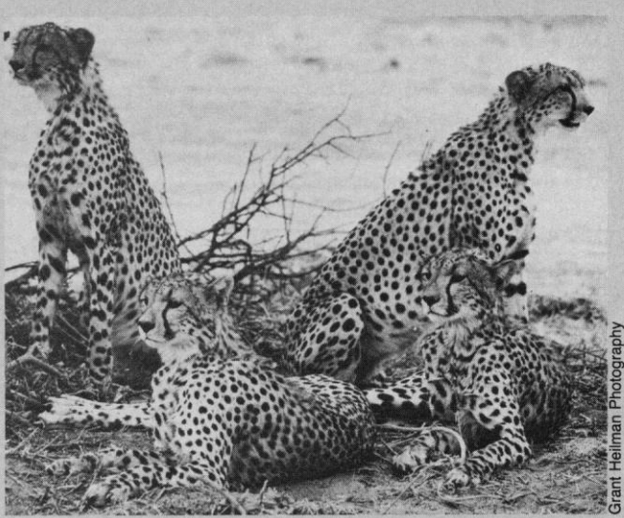
Prior to 10,000 years ago cheetahs lived in many parts of the globe but they are now restricted to just two zoogeographic areas, southern and eastern Africa. This dramatic contraction of range, which was suffered by many African mammal species at the end of the Pleistocene Ice Age, was in cheetahs apparently accompanied by an equally dramatic series of bottleneck events, which probably brought the species close to extinction on a number of occasions.

During the past several years, Stephen O'Brien, of the National Cancer Institute, and colleagues in the United States, the United Kingdom, South Africa, Kenya, and Tanzania, have been examining the cheetah's status and have come to the remarkable conclusion that the extant populations are even more genetically uniform than laboratory inbred mice. So genetically uniform are these animals that completely unrelated individuals within the southern African population can accept skin grafts without immunological rejection, a remarkable state of affairs that O'Brien and his colleagues reported in *Science* in 1985.

O'Brien and his colleagues now report a comparison of the genetics of the southern African population, which is designated by the subspecies name *Acinonyx jubatus jubatus*, with animals from East Africa, which are given the subspecies name

Kenyan cheetahs

Genetic data show the East African species to be slightly more genetically variable than the South African population, but nevertheless are severely genetically impoverished.



Grant Heilman Photography

Acinonyx jubatus raineyi. It turns out that the East African cheetahs are more genetically variable—if the existence of two polymorphic loci out of 49 tested can be called variable—than the southern subspecies. This can be interpreted, suggest O'Brien and his colleagues, as evidence that after suffering a severe bottleneck in the distant past, the population split into the southern and eastern subspecies, with the southern population suffering a second bottleneck, possibly at the hands of 19th-century farmers, who slaughtered thousands of animals.

The electrophoretic data that O'Brien and his colleagues examined is a measure of additive variance (see main text), and what they see is just a small fraction of the variance exhibited by most large African mammals. This level of genetic homogeneity in the cheetahs, say the researchers, is a clear indication that the original bottleneck was severe and prolonged. A single bottleneck would simply not have eroded the additive variance to this degree, even in a large animal whose potential rate of population increase is limited.

O'Brien and his colleagues note that breeding success with captive cheetahs is typically very poor, both because of the very low quality of the male's spermatozoa and the unusually high infant mortality, both of which are indications of genetic homogeneity. This might be improved, they say, by including both southern and eastern African animals in breeding programs, as the minimal genetic distance between them really precludes thinking of them as true subspecies. ■ **R.L.**

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