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Genetic conflict within the individual

Abstract

In the great tradition of Ernst Mayr, Austin Burt and I humbly attempted to master the entire literature on within-in genetic conflict in all species except bacteria and viruses (Burt and Trivers 2006). It took us 15 years and here I provide a brief glimpse of some of what we learned (missing references can be found in our book). The subject is very large and intrinsically important because within-group conflict is well-known in various other contexts – societies, sexes, families – to produce very important effects that are easily overlooked, or misinterpreted if conflict is denied or unrecognized. Why should the same thing not be true for within-individual genetic conflict? What aspects of our reproduction and phenotype are we missing by not understanding internal genetic conflict?

There are two main sources of internal genetic conflict. One involves different degrees of relatedness by different genetic elements within us (e.g. Y chromosome, mtDNA) to related individuals. The other involves drive, the differential replication of genes into the next generation. The importance of the first kind of conflict for ourselves is found in genomic imprinting, the fact that some genes are paternally active, with their maternal copy silenced, and vice-versa. Such genes evolve to support patrilines and matrilines respectively. Conflict concerns early development, with paternally active genes acting to garner more resources, often resisted by maternally active ones. Conflict also concerns adult behavior where such behavior effects relatives differentially related through one parent or the other. We literally have a paternal self and a maternal self and they are often in conflict.

Drive is a ubiquitous force in nature, found in all (or almost all) species. A classic case of drive is found on the 17th chromosome of the mouse in which a special form, the *t*-haplotype in males shows strong drive (90% transmission) in single matings with females. It shows no drive in females and this sex difference is expected to result in the relative deterioration of the *t* female's phenotype, as indeed appears to be true. The *t* was put together over roughly 3 million years, through the acquisition of

4 non-overlapping inversions, containing driving elements and a resistance gene that largely prevents the drivers from harming the *t* itself.

Homing endonuclease genes (HEGs) are another example of drive, found in single-celled organisms. They drive by cutting their paired chromosome at the same spot where they reside, causing the double-strand repair machinery to use the HEG as the template to fill in the missing DNA, thus making the HEG double in number. HEGs survive over evolutionary time via horizontal transmission between related species and they have been selected to target very conservative sections of very slowly-evolving genes. HEGs in the lab spread under outbreeding but not under inbreeding, a widespread rule for selfish genes, shown also for B chromosomes. HEGs can also be engineered to attack pest species, such as mosquitos bearing malaria. A similar novel attack on a pest involves introducing a siDNA into HIV causing it to commit suicide.

Transposable elements spread within a genome by making additional copies which they insert elsewhere, a process that can be repeated by both elements indefinitely. A veritable zoo of transposable elements have evolved and together they tend to inflate genome size. Our own genome, for example, consists of at least 50% transposable elements or their remains. Genome size, in turn, is correlated with a high risk of extinction in both plants and reptiles and appears to have sharply reduced intellectual development in the large-genomed salamanders, by greatly increasing size of brain cells so that fewer can be fitted into a given space.

Dedication to the memory of Ernst Mayr

It is a pleasure to dedicate this talk to the memory of Ernst Mayr who was a close friend of mine for almost 40 years (Figure 1). He had the strongest phenotype of any organism I ever met, man or beast. Until he was 50 years old he had, as he told me, a photographic memory. That is to say, one look at a page and everything was put into his memory. He said he kept it a secret because for one thing it gave him a "rather unfair" advantage in the German educational system, based heavily as it was on rote learning and memory.

But his once-perfect memory was still good enough in his 60s so that he was able to give me the key reference for understanding the evolution of sex differences, my most cited paper "Parental investment in sexual selection". I had been taking a reading course from him in genetics and one day I had not done my reading so I told him pigeon stories instead which had some of the elements of my thinking on parental investment. After a while he said, "Have you ever read Batemen '48 in *Heredity*?" I said no. He suggested that I should do so, that it had important implications for my thinking. A couple of weeks later, still not having done any genetics, I

returned to Dr Mayr's office and dared to tell him some more pigeon stories. After a few moments he cut me off, leaned forward and said, "Have you *yet* read Batemen '48 in *Heredity*?" I answered no. I had in fact entirely forgotten Dr Mayr's suggestion. Then he did something that I will always love him for. He looked across his table and said to me: "I will not continue this conversation until you have".

I left Dr Mayr's office with one burning desire in life–to read Bateman '48 in *Heredity* and that night with my body bathed in the odious green light of the Xerox machine of that time I copied Bateman '48 in *Heredity*. And later that night the scales fell from my eyes. Because Bateman had something that no one else had including myself. He had variance in reproductive success analyzed separately for the two sexes. Incidentally, no one else in biology interested in sexual selection knew of this paper until my paper brought it to light.

Ernst was also a strong moral individual and it is very important in life if you can find someone stronger than yourself so that you can defer to that person and have someone to hold on to when you need balance. Ernst performed that role in my life. When I visited him in his office in 1992 I complained that of all 21 full professors at the University of California at Santa Cruz I had the slowest rate of advancement. He leaned forward toward me and growled "I vould have fired you!" This was very bracing – and not entirely undeserved!

He was also a very loving man, for example with his wife Gretel whom he took care of during the last three months of her life. I remember one evening in his home where he mentioned that he had translated a paper from German when his wife Gretel cut him off and said to him "But Ernst, it was *I* who translated that paper." Then she turned to me, "You know, Ernst and I are like one, Bob, but still it was *I* who translated that paper." Ernst had a very sheepish look on his face and for the next ten years he never referred to that paper without adding (whether she was present or not) "which my wife so kindly translated for me".

Finally, Ernst believed in big projects. He believed almost that it was the duty or "Pflicht" of an evolutionist to consider biological problems in their broadest aspects, that is, across a great diversity of organisms the better to see the general principles. Thus he wrote a book on *Animal Species and Evolution* covering the entire topic in all animal species (Mayr 1963). But he also believed in the importance of drawing boundaries. I once asked him why he had not included plant species and simply called his great book "Species and Evolution" and he said that people had often asked him that question but that he believed that plants provided a special set of problems in which he was not expert and though the species were fewer the material was not as easily mastered for him as the animal work.

And in our own humble way I believe that we have tried to follow his lead in both regards. In the work I will describe we try to take a very general view and see all

cases of internal genetic conflict in all species of plants and animals, with an eye always for general principles that may help bind the subject together. The project ended up consuming 15 years of two scientists' lives (Burt and Trivers 2006). We also had to draw our own boundaries. Just as Ernst left out plant species so we left out bacteria and viruses. I remember once talking ten years ago to a prominent student of bacteria and he asked me how we intended to cover bacteria. I answered, "Not at all". His face fell. "But Bob, bacteria are half of all of life." I answered, "That's precisely the point. We are barely able to cover the other half. With bacteria, we will never finish."

Truly selfish genes

Truly selfish genes are defined as those that spread in spite of the fact that they inflict a cost on the organism itself, that is, on most of the rest of the genotype within which they reside. So far we can see only two broad categories of selfish genes, or more precisely, selfish genetic elements (since they can be genes, parts of genes, entire chromosomes and so on). One category refers to differences within the genotype in degree of relatedness to other individuals. For example, the Y chromosome in a man is always found in his son but never in his daughter. A gene on the Y favouring sons and giving no thought to the interests of daughters would be expected to spread but if it did so it would thereby harm the X chromosome and the autosomes (all the non-sex chromosomes), none of which compute this degree of relatedness. So they would evolve to resist or suppress the actions of the Y.

Conversely, the male's X chromosome is found only in his daughters and would be expected to favor them at the cost of sons (with the Y and the autosomes in disagreement). And the X chromosome is relatively large with well more than a thousand described genes while the Y is small, mostly inert with only about 80 genes described to date. In any case, we know of no good examples of a selfish X or Y chromosome in a male animal biasing behavior to its offspring in the way just imagined. Perhaps the far more numerous autosomal genes determine outcome (they are equally related to offspring). More generally, degree of relatedness (r) for any gene is the chance that it will be found in another individual by direct descent from a common ancestor.

For our own species the most important kind of conflict between the different genetic elements that make up our genome (X, Y, autosomes, and mtDNA) is the conflict between our maternal and paternal genes, that is, those we inherited from either mother or father. It turns out that a small minority of our genes have the unusual property that their activity in us depends upon which parent donated the copy. So the maternal copy may be silent and the paternal active or the other way around. Such

genes are said to be imprinted since something in addition to the DNA determines whether the gene is expressed. (As we shall see below methylation of cytosine residues appears to be part of the mechanism.)

A second category of selfish genetic element causes drive. Drive refers to the tendency of a gene to be found in offspring at a higher rate then expected according to the "free, fair" laws of Mendelian genetics: for a typical autosomal gene, the expected chance is ½. Some genes are capable of improving on this probability and are found more than ½ of the time in the offspring. This category can be divided into two major sub-divisions. In one case genes increase in frequency at a given locus only. In the second genes increase in frequency by colonising new loci, that is, making copies of themselves which are placed elsewhere in the genome which copies are also capable later of adding more copies to the genome and so on. These so-called mobile genetic elements make an important contribution to the genetic architecture of many species including genome size itself.

In the view that prevailed in the 1980s in most areas of biology selection acted always to improve the phenotype of the actor where this was understood as increasing the individual's reproductive success (number of surviving offspring) or better put inclusive fitness – that is, genetic reproductive success (including effects on relatives, each devalued by the appropriate degree of relatedness). Under this "phenotype paradigm" there were imagined to be only three kinds of genes: positive, negative and neutral. Positive genes were those that had positive effects on the phenotype; they increase in frequency. Negative genes have negative effects and decrease in frequency. And those that have no effect – are neutral – perform a random walk over time. The phenotype paradigm implicitly assumed that there was no within–individual genetic conflict. Animals, at least, were imagined to consist of a set of genetically identical cells working for the gonads and, as we later came to understand, for the gonads of closely related individuals as well. We now know that even the assumption of genetically identical cells is not always true. But more importantly we see that there can be genes whose effect on the phenotype is negative but which spread because they give themselves a benefit in propagation. One can also imagine genes that are in fact beneficial for the organism but for some reason "drag", that is, replicate slower than expected, perhaps in competition with driving genes. These genes may be lost even though they are phenotypically beneficial. Let us begin our account with the special case of human cell chimerism.

Human chimerism

There are some dramatic examples of imperfectly related cells within the human body (Figure 2). A woman is found genetically not to be the mother of her own children even though she gave birth to all of them. The reason appears to be that she

had a co-twin when she was in her mother's womb who died early in development but not before this twin had sent her primordial germ cells to invade her sister's ovaries (Figure 3, bottom). So when her sister grew up her ovaries consisted of her sister's ovaries and thus the women gave birth to her own nephews and nieces. It is completely unknown how frequently this occurs in humans. This particular case only came to light because the woman applied for governmental family assistance and was required to prove she was genetically the mother of the children for whose support she applied, at which time she discovered that she was not the genetic mother of her own children. But we do know that in some animal species this is a common occurrence with important social effects. For example in New World monkeys such as tamarins and marmosets in which twinning is very general, it is common for females to have bodies that are composite of their own cells and those of female co-twins (with both twins often surviving until birth). This results in a female being relatively less related to her own offspring which under certain conditions can make it more likely that she would choose to help her (putative) mother reproduce instead of reproducing on her own.

Another case of human cell chimerism is far more general. Fetuses typically place some of their cells into their mother (Figure 3, top). Here they migrate to a variety of tissues, including the thyroid, lymph tissues and the brain. In some cases they have been shown to endure for at least 28 years. Whether they ever act on behalf of the offspring that donated them is unknown – for example, by increasing mother's nursing for the first two years after the offspring's birth. In mice fetal cells have been shown to migrate to injured areas of the mother's brain and here they may provide stem cells or other elements of repair.

The *t*-haplotype in mice

About 80 years ago it was discovered that there are two forms of the 17th chromosome – the regular 17th and an uncommon form, the so-called *t*-haplotype. In a male with the two chromosomes (that is, having one of each) the *t* is found in 90 percent of his offspring in single matings with females (Figure 4). The *t* does this trick by somehow disabling the sperm cells that contain the other chromosome. The *t* produces a developmental poison to which it itself has the antidote. The development of the poison causes sperm cells with various defects. In some cases they fail to swim in a straight path and swim instead in spirals. In another case they suffer from premature acrosome reaction in which the chemicals at the tip of the sperm packed into the acrosome – whose function is to digest the outer cell membrane of the egg thereby permitting sperm entry – are released prematurely before the sperm reaches the egg. If it then reaches the egg it will have nothing with which to gain entry.

Like many other driving elements the *t* drives only in one sex. It shows normal transmission in females. This sex bias in drive has an interesting consequence. Normally the net effect of a sex-antagonistic gene (that is, one whose effect in males is positive and effect in females is negative, or vice-versa) has to be positive for it to spread, that is, the benefit in one sex must exceed the cost in the other. But this is not true for genes located within driving elements. Imagine a gene that increases male survival by ten percent but decreases female survival by fifteen percent. Normally such a sex-antagonistic gene would be selected against but if the gene is located within the *t*-haplotype then the ten percent gain in survival in males is nearly doubled by the drive in males while the fifteen percent cost in females remains unaffected. Thus, the phenotype of the *t*-male is expected to improve at the expense of an even greater deterioration in the *t*-female. The evidence is consistent with expectation. *t*-females are less symmetrical, less fertile, and less dominant than normal females, while *t*-males perform similarly to normal males except that in some situations they appear to be more dominant.

The *t*-haplotype has grown in size over roughly three million years to become one percent of the mouse's genome. We know that this was achieved by adding successive inversions which locked genes into tight linkage with each other, preventing recombination between the *t* and non-*t* sections of the 17th chromosome (Figure 5). Each of these inversions typically has a gene (D) that adds to the degree of drive so the drive itself is a result of at least 3 (and probably more) genes along the *t*-haplotype acting together to disable the alternative sperm cell, along with a "resistant" gene (R) that prevents the *t* from disabling its own sperm cell. The suppression of recombination sharply reduces genetic diversity on the *t*. It can still recombine when paired with a second *t* in a female (*t*/*t* males are sterile) but such females are rare and show low reproduction when they do survive. In principle, the loss of recombination has negative consequences for the rest of the genome, 1% of it is (in addition to the Y) evolving as an asexual entity in a sexual species.

A recent parallel case of some interest has been discovered in monkey flowers (Fishman and Saunders 2008). Here drive occurs in females and transmission is normal in males. First uncovered in crosses between related species, where drive is very strong, a weaker form of drive was soon discovered within a species. This incidentally is a common feature. Within a species, a driving element will have been selected for resistance, which should reduce its level of drive. Between species, the victim may lack any history of encounter with the selfish elements and defensive elements. What is striking is that the cost appears – as with the *t*-haplotype – in the opposite sex that drives, namely, male fertility is reduced by roughly 20% in homozygous drivers and this approximately balances the 58% drive seen in females. But note also that the effect is measured only in the homozygotes. There are similar

cases of sex-antagonistic effects and drive, especially in B chromosomes, but so far little evidence of a widespread effect (Burt and Trivers 2006).

A general principle worth noting here is that the spread of selfish genes within the individual leads to generative effects on individuals. That is, a selfish gene may initially inflict a cost but by its evolutionary dynamics it will come to inflict additional costs. Thus the driving *t*-haplotype initially inflicts the cost of double recessive action in which the mouse is either dead or if a male, is sterile. But as time goes on the *t*-haplotype inflicts a sex-antagonistic bias lowering the average fitness of a *t*-haplotype male and female and entrains a growing non-recombining element in a larger sexual species. This is a general principle that we encounter over and over in this subject: the spread of selfish genes tends to entrain negative effects at higher levels, both in individuals and even species.

Homing endonuclease genes

Homing endonuclease genes (HEGs) are genes that spread by a simple means of drive within a species and they are also selfish genes that are designed to colonize related species. Indeed their long-term survival depends upon this ability to achieve horizontal movement between species. A scientist who has worked extensively on homing endonuclease genes is my co-author Austin Burt (Figure 6). HEGs are found in relatively simple creatures such as fungi, including yeast, and other single-celled organisms. HEGs have a simple mechanism of drive as can be seen in Figure 7. The HEG produces an RNA which generates a protein which returns to the same site on the paired chromosome – homes in on a recognition sequence, so to speak – and cuts the chromosome. Along comes the double-strand repair machinery, it sees that DNA is missing from both strands so it looks to the complementary strand of DNA to see what is missing and then copies this missing stretch. In other words it copies the HEG itself (Figure 7). At the end of the process the homing endonuclease gene is found in two copies where formally it was found in only one. HEGs are usually found within self-splicing introns or inteins, meaning that they do not disrupt protein function and their only cost to their host appears to be the cost of replicating them every generation (~1000bp of DNA). A very dramatic picture of a HEG protein at work cutting double-stranded DNA can be seen in Figure 8. This is perhaps the most exact picture we have of a selfish gene in action. Note that as an intein, the larger protein in which the HEG protein is based has separated out and will be completely functional.

Where did the first copy come from? We now know that the first copy arrives horizontally, that is, from another species via some kind of a vector (perhaps a virus). When phylogenies of HEGs are compared with those of the species they occupy,

the phylogenies do not match up, which implies horizontal movement (Figure 9). If horizontal transmission is the way to stay alive over evolutionary time, that is, colonize new sites, then HEGs should show adaptations for horizontal transfer. For example, if a HEG tries to move from one species of yeast to another related species it will need to find the same recognition site to home in on and insert itself in the first place. And it must be a recognition site which its own protein is capable of cutting. In short, homing endonuclease genes are expected to attack relatively conservative genes across a group of organisms.

In yeast (*Neurospora*) the gene that a particular HEG (*VD1*) attacks is relatively invariant in genetic composition across a group of related species compared to a random set of genes (Figure 10). When one then looks at the actual gene that the HEG targets, the site at which the HEG cuts is in turn the slowest evolving site over the entire stretch of the targeted gene. In other words HEGs have been selected to target very conservative, slowly evolving sites in its host species precisely because only these HEGs were able to move between related species and stay alive through evolutionary time. Within a single species it rapidly drives to fixation, at which point everybody has two HEGs at that site and there is no more drive. (Unlike transposable elements, HEGs do not move within the genotype.) Since HEGs are often associated with introns or inteins they have only a tiny negative effect on the phenotype of their host, but a HEG can be said to die over evolutionary time in the sense that mutational decay sets in immediately when every one is homozygous for the element. At a certain point, estimated to be on the order of one million years, the HEG will degenerate to the point where it can no longer drive even if transferred to a species with an available site. Thus a crude estimate is that a HEG must move at least once every million years to another species in order to stay alive. It is assumed that HEGs are restricted to unicellular organisms because these permit transfer between related species via a vector much more easily than do multi-cellular species.

This does not mean, however, that HEGs will not work perfectly well in multi-cellular creatures at least when one or two design elements are added to them. This possibility spurred Austin Burt to propose that engineered HEGs might be introduced into pest species like mosquitoes bearing malaria in order to decimate mosquito population numbers. It is necessary to design a HEG that targets a section of an important gene in the mosquito, one whose effects are dominant and where most individuals initially are double dominant (Figure 11). When the artificial HEG is introduced into the new species (mosquito) it will begin to spread rapidly since it is always found in the heterozygous state at which time it drives. But as its frequency increases so do double homozygous individuals both of whose copies of the vital gene are interrupted by the driving HEG, resulting in early death. Thus as the HEG spreads it should start to decimate the population within which it is spreading – by 80% in 15 generations under simple assumptions (Figure 12).

The major expected problem of course is co-evolutionary adaptations of the host genomes that interfere with or even stop the driving element. There will be a very strong selection pressure to evolve precisely these kinds of defences. On the other hand Burt has shown that it is easy to increase the power of the attack by an order magnitude by simultaneous attack with more than one HEG, or to limit the lethal effects to females only, which will roughly triple the desired effect, or by increasing drive to, say, 99% and so on. The Bill and Melinda Gates Foundation has supported this work and recently a team of scientists has managed to engineer a HEG that can be introduced into the fruit fly *Drosophila* where it then shows drive. Since this is a species closely related to mosquitoes the proof that engineered HEG drive is possible in them is an important step forward.

Blocking HIV replication by causing HIV to commit suicide

HIV is notoriously difficult to target via a vaccine because the virus mutates at a very high rate so as to change its coat proteins in such a way that no sooner does one learn to mount an immune reaction to a given coat protein then it has mutated to a different form. This suggests that a direct attack on HIV may provide more promise. In a distant parallel to controlling pests through engineered HEG drive, Mölling (2008) (Figure 13) has suggested that by introducing a siDNA into the environment of HIV – for example in a vaginal crème or in an injection within a day or two of unprotected sex – and waiting for this to be taken up by HIV, one may be able to cause HIV to commit suicide. Normally a single strand of HIV RNA replicates by acting as a substrate for the assembly of a complementary DNA strand after which the RNA strand is broken up, thereby permitting the DNA to act as a template to form its complementary strand (Figure 14). Normally the molecule doing the cutting of the RNA, so-called RNase H, does not cut the single strand of HIV RNA until the complementary DNA has been produced. But by introducing the siDNA one can cause the early activation of RNase H such that the RNA is cut into pieces before it has acted as a template for a DNA strand (Figure 14). In short, the HIV has been induced to commit suicide. Mölling guesses that even in a vaginal crème applied prior to sex the HIV would be killed off before it could enter a woman's body but she regards a safer therapy as injecting large amounts of the siDNA into the blood within 24 hours or so of sexual relations. It should be emphasized that these siDNA are trivial pieces of DNA which the body is in principle well used to so no side effects of this treatment are expected. Note that Mölling's system does not involve drive but it does involve a small, engineered piece of DNA of the kind that is normally used (siRNA) to regulate development and in conflict situations between different elements of the genome (as in suppressing transposable element activity). So

we can use both drive and molecular components of conflict situations in organisms to design major attacks against diseases that have proved resistant to other means of defense.

Inbreeding inhibits the spread of selfish genes

HEGs can also be used to study the effect of the breeding structure on the spread of selfish genetic elements. As can be seen from Figure 15 when a HEG is introduced into a lab population at a 20% frequency this frequency remains, under inbreeding, unchanged for five meiotic generations while it triples in frequency under outcrossing. The logic for this relationship is very simple. Under inbreeding (or asexual reproduction) inbreed lines (or asexual ones) compete with each other through evolutionary time and those lines which are relatively free of selfish genetic elements should be those that do relatively well since they suffer less cost at the individual level. They should crush those inbred lines that happen to have higher frequencies of selfish genes out of their shared ecological space. This truth has been verified with a variety of other kinds of selfish elements. For example, B-chromosomes are extra-numerary chromosomes found in some individuals but not all and hence by definition unnecessary for normal development. In fact, they are typically harmful to the phenotype but spread through drive. A careful analysis of 353 species of British plants whose breeding system was known shows a very strong association between outbreeding and frequency of B-chromosomes (Figure 16).

I remember when I first realized many years ago that selfish genes are a disease of outbreeding. You could have knocked me over with a feather. As a long time outbreeder myself – my bias being the more a woman differs from me in appearance the better for me – I had always assumed that selfish genes were yet another negative effect of inbreeding. But the logic is clear. In order to survive over evolutionary time selfish genes are colonizers. They are always looking to colonize fresh genetic individuals lacking themselves, to escape their own destructive effects. Not only do they colonize new individuals within species but they colonize new spaces within the genome and colonize new species through horizontal transmission (usually via a vector).

Genomic imprinting: our paternal and maternal halves are in conflict

In the 1980s a hitherto unsuspected subtlety of our genetic system was revealed. Before then it had been assumed that a gene expresses itself the same way in an individual regardless whether the gene came from the mother or the father. After all if

it was the same DNA structure why should it not act identically? It was then discovered that maternal and paternal genomes are not equivalent and that for normal development in the mouse (as well as humans) you require one set of genes that have come from each parent. They cannot, for example, both have come from males. By 1990 the first two imprinted genes in mice were described, *Igf2* an *Igf2r* (Figure 17). *Igf2* causes faster cell replication and greater growth of a mouse fetus *in utero*. It is paternally active. That is, only the paternal copy of the gene is active, the maternal copy has been silenced. The effect of the single paternal *Igf2* is to increase the size of the fetus at birth by 40 per cent. The gene is partly opposed by the action of *Igf2r*. This gene produces a general scavenger molecule that picks up chemicals no longer needed in the cytoplasm and deposits them in the lysosome where they are digested. *Igf2r* has evolved a secondary binding site in mammals for *Igf2*. Thus, it binds to *Igf2* and carries *Igf2* into the lysosome where it is destroyed. In fact, 70 per cent of the *Igf2* gene product is eliminated by *Igf2r*. This gene is maternally active, the paternal copy being silent. Its effect is to reduce the size of the fetus by 30 per cent at birth. Since numbers are small we cannot tell whether the 40 per cent gain by *Igf2* is the same size as the 30 per cent loss due to *Igf2r*. As we would say in the United States, "this is a strange way to build a railroad". That is, why build an organism that overproduces a chemical at cost to itself only to turn around and destroy the bulk of the chemical at additional cost. Such inefficiencies are the hallmark of conflict and indeed *Igf2* and *Igf2r* act as if they are in conflict. Let us see if we can understand why.

Consider degrees of relatedness (r's) between yourself and your maternal half-sibling (see Figure 18). Under the old way of measuring degrees of relatedness, we would have said that for any typical gene in you there is a half chance that it is found in your mother and, if so, a half chance that she passed it to your half-sibling: ½ x ½ = ¼. Your degree of relatedness to your half-sibling through the mother is thus 1/4. But with genomic imprinting – that is, with the ability of the gene to express itself preferentially according to parental donor – we can split the average r we have just computed into two parts. For a paternally active gene, we know that it came from father and cannot be found in the maternal half-sib, which is fathered by a different (presumed unrelated) male. By contrast a maternally active gene certainly came from mother and has a half chance of being found in the half-sibling. Thus, genomic imprinting splits an average ¼ r into ½ and 0. These may not sound like big differences but remember the available spaces between 0 (unrelated) and 1 (identically related), so the difference between ½ and 0 is substantial indeed.

Consider the relevance to fetal conflict within the womb. Imagine a series of fetuses each fathered by a different male but each growing inside the same mother. Maternally active genes will see each other as related by ½. By contrast a paternally active

gene will see all other fetuses as unrelated and its mother as well. Unless its mother mates with its own father in the future the paternal gene has no overlapping self interest with its mother's future reproduction. Thus in this extreme situation where all of the siblings *in utero* are related by 0 on their father's side we expect extremes of selfishness where paternal genes lead each fetus to fight for the maximum of beneficial resources, no matter what the harm is to its sibs, both past and future. By contrast maternally active genes will value their sibs by ½ and their mother by 1. Paternal genes ask for more and maternal for less and unimprinted genes are intermediate between the two.

Of course, in nature we do not often expect to find this extreme situation but we do always expect to find paternal relatedness within the womb on average to be lower than maternal relatedness. In nature we know that almost half of all litters are fathered by two or more males. This means, on average, that paternal genes will be selected to act in their narrow genetic self-interest to the detriment of both maternally active and unimprinted genes. Thus, the pattern we have described with *Igf2* and *Igf2r* fit the kinship argument perfectly, a paternally active gene more demanding of maternal resources *in utero* while the maternally active one largely counters these effects.

Almost 100 imprinted genes have been discovered in mice now (and perhaps two thirds as many in humans). About half of these affect early development, many according to the rule, paternally active genes increase maternal investment while maternally active genes have the opposite effect. For example, one gene (*Rasgrf1*) is active during nursing and apparently increases nursing activity so that offspring weigh more at weaning. The gene is paternally active. Thus many early-acting genes support the underlying kinship argument we are advancing for genomic imprinting. But what about later acting genes? These, it turns out, often affect the nervous system and/or adult behaviour. Here kinship considerations may also be important.

Let us consider an example where the facts are clear. There are two paternally active genes that influence maternal behavior in mice (*Peg1/Mest* and *Peg3*). For example, they increase maternal cleaning of the young and huddling over them to keep them warm. Why should maternal behavior be entrained by paternal genes? Adult female mice typically live in a world of close relatives, especially sisters, with whom they may share reproductive activities. They will inevitably be more related to these female relatives through their mother than through their father. Thus, maternal genes in a female mouse will balance effort expended on personal reproduction with effort expended to help their maternally related kin. But paternal genes will tend to place much greater weight on personal reproduction, since they are primarily (or only) related to their progeny and to no others (Figure 19). One can even imagine an internal argument in which paternal genes say "Let's go all out for our own children"

while maternal (or unimprinted) ones may say, "But what about sis' sick child, let's help her first."

The notion of such internal conflict is supported by work on mouse chimeras, in which the mouse is a mixture of typical cells whose genes come from both a father and a mother and either cells with doubly paternal genes or doubly maternal ones. Such cells are produced in the lab by adding two pronuclei from sperm to an egg lacking a pronucleus or by adding a maternal pronucleus to an unfertilized egg (Figure 20). Although pure such forms die early, when the cells are mixed with normal cells one can produce a surviving mouse which is chimeric (Figure 21). Two correlations are worth mentioning. The more a chimera has doubly paternal cells the larger it is at birth (as expected: Figure 22A). What was not predicted was that brain size would shrink while body size increased (Figure 22B).

Note that doubly paternal cells do not do well in the neocortex which is such a large section of the brain that the absence of such cells shows up as a shrunken total brain (Figure 23). But doubly paternal cells do well in the hypothalamus while doubly maternal ones do not. Thus, one can easily imagine an internal argument in which the neocortex in effect, says "I care for family, I believe in family, I am going to invest in family" and the hypothalamus says "I'm hungry". In other words the maternally active genes act on behalf of the larger (maternally related group) while the paternally active genes act for the individual's personal reproduction.

Another example of potential internal conflict concerns the problem of mating with your first cousin, related on average by $1/8^{th}$. But of course you are usually related through one parent only. If it is your mother's brother's son and you are deciding whether to breed with him, then your maternal genes will see the cousin as related by $1/4^{th}$ and therefore the gain in relatedness of mating with him instead of an unrelated male as $1/8^{th}$ (from ½ -> $5/8^{th}$) against which must set the cost of inbreeding itself, measured as a reduction in the quality of the phenotype of the inbred individual, perhaps on the order of 5%. But the paternal genes will see the other individual as unrelated. They will see no gains in relatedness to any resulting offspring. They will only see the costs of the inbreeding itself. Thus, one can easily imagine a situation in which one's maternal genes argue in favor of the copulation – "kissing cousins are cute" – while your paternal genes take a moralistic stance and emphasize the cost to any offspring thereby produced. Naturally the logic is reversed for relatives related through the father. Even a child forced into incest by her father may experience some internal ambivalence, even if both sets of her genes are harmed, for her paternal genes may still act to hide the father's transgression for his sake.

Although it has been long believed that the total of imprinted genes would be around 200 in mice and somewhat less for humans, we really have no idea what the total is for either species. What seems certain is that we do have a maternal and a paternal

self and that they may disagree over many details of our behaviour. Take, for example, the problem of discounting future effects vs present ones – to what degree, for example, do we value chocolate today compared with more chocolate tomorrow? It is easy to imagine that our maternal and paternal halves may have different optima regarding discounting. Genes involved in social interactions may prefer to save benefits in the future for general sharing while genes involved in purely egoistic functions such as growth may prefer the chocolates right away.

David Haig (Figure 24) who has suggested many of these ideas has also argued that it may be possible for a limited kind of reciprocal altruism to evolve between oppositely imprinted genes, so that, in effect, paternal and maternal genes may develop to split the difference between their alternative viewpoints in order to diminish the amount of wasteful internal conflict (Haig 2003). This is, at present, only a theoretical possibility.

Transposable elements

Transposable elements are special genes that have the capacity to make extra copies of themselves and place these elsewhere in the genome. That is, they move horizontally within a single genome over time. There are two main classes of transposable elements – those that use a DNA intermediate and those an RNA intermediate. Figure 25 shows an example of a DNA-transposon (*Ac*). After the replication fork passes through the selfish gene one copy of the two copies jumps ahead of the replication fork on the same chromosome so that it is replicated a second time. It goes from two expected copies to three. The trick is to detect when the replication fork has passed through you, then jump but be sure to do so quickly and land ahead of the moving fork.

By contrast, as we see in Figure 26 a *LINE* element produces an RNA which produces a protein which binds to the RNA. The protein manages to nick the target DNA elsewhere in the genome and reverse transcription permits a DNA copy to be recreated from the RNA so that a new *LINE* element is integrated elsewhere in the genome. Both DNA and RNA transposition can be repeated at their new location so that, other things being equal, the gene tends to increase geometrically in frequency over time. Transposition rates are perhaps usually on the order of 1 per 1000 meiotic cycles.

The result is often a genome that is rich in transposable elements many of which are no longer active. That is, they are unable to transpose on their own power though they may be able to use the transposases produced by others to move themselves. A glance at the human genome shows that roughly half of the entire genome (Figure 27) consists of transposons or their fossils (remnants of transposable elements that are

now no longer functional). This is surely an underestimate – in part because as we travel further back in time it is more difficult to spot a remnant transposable element, due to the intervening, inevitable mutational decay.

Although it is still sometimes doubted that transposable elements are truly selfish, so that people still try to find functions for the elements at the level of the individual, there can be little doubt that they are almost always harmful. Figure 28 shows that for each additional *P*-insertion on the *X*-chromosome of a male *Drosophila* there is (on average) a reduction in survival of the individual with the insertion.

That the spread of transposable elements can also have effects at the level of the species seems all but certain. The general effect of the spread of selfish elements is to increase genome size. For example, in the past 6 million years the genome of maize has doubled in size compared to its closest relative sorghum and this was due entirely to a burst of transposable activity in maize. Genome size in turn is a variable that has important effects at the level of species. As Vinogradov (2003, 2004) has shown, the larger the genome the greater the chance that a species will be Red-listed, that is placed on the list of species that are about to go extinct. In plants genome size of Red-listed species is twice as great as that of species not at risk of extinction and this effect is highly significant. A similar effect over a much smaller range of genome size can be found in reptiles (see Figure 29). If these increased genomes are in part due to the spread of selfish genes then we have dramatic evidence that selfish genes can not only affect individual survival but actually affect species survival as well.

A look at genome sizes among vertebrates will highlight another dramatic effect of genome size on trans-specific evolution (Figure 30). Notice that bird genomes on the right half of the graph are very small, reptile and mammal genomes somewhat larger and bony fish to the far left very small, while in between salamander genomes are enormous. The reason for this enormous size is unknown. Polyploidy is frequent in salamanders but removing polyploidy has little effect on overall salamander genome size. So far, no work has appeared on the relative frequency of transposable elements in salamanders. But let us assume for a moment that it is selfish genes that have inflated salamander genome size. This inflation has had a dramatic effect on the nervous system. This is because there is an invariant, positive relationship between genome size and cell size. Larger genomes produce larger cells. This is true for every cell category known including neurons. Large genomes imply large brain cells which means fewer available to fit in a given-sized brain. If a salamander's genome size is 40 times that of a related species then its brain cells would on average be about 10 times larger, meaning only 1/10th as many can fit in the brain. Even miniaturized salamanders selected to live in such small habitats as earthworm holes neither reduce their genome size nor the relationship between cell size and genome size. These

two variables seem invariant. Instead the species tend to increase the size of their heads relative to their bodies and often do away with one of two sensory modalities, smell for example in order to concentrate on sight. The result is a brain structure so simple that anatomists first describing salamander brains in the 1940s said they would have argued that salamanders were primitive to all other vertebrates including fish, if they did not know better (Figure 31).

Mayrian Summary

Let me give a summary of this talk as Ernst Mayr might have (Figure 32). "In biology zer is mechanism and zer is meaning. Mechanism is how ze machine works. Meaning is why it works zat way. Mechanism is what molecular biologists study. Meaning is what evolutionary biologists study. We try to understand ze meaning of ze mechanism."

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Figures

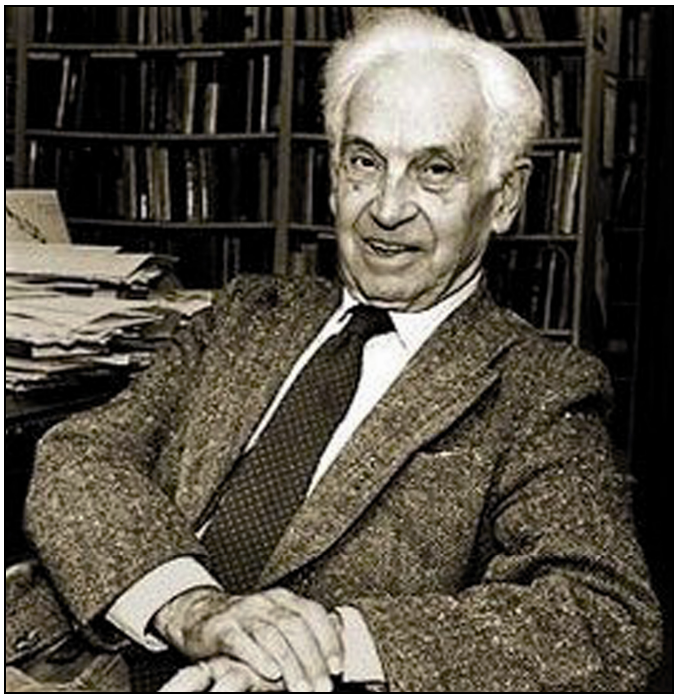

Figure 1
Ernst Mayr (1904–2005) in his Harvard Museum of Comparative Zoology office.

DNA NIGHTMARE FORCES MOM TO BATTLE FOR KIDS

She's one of only 30 people in the world with two identities in the *SAME BODY*

MOTHERLY LOVE: Lydia with her brood of four, and reunited with their dad Jamie

LYDIA FAIRCHILD had to wage a court battle to keep her own children – because DNA tests "proved" they weren't hers!

Shockingly, DNA samples from her mouth swab didn't match the DNA of her children, but DNA from a cervical smear DID.

And after a sympathetic lawyer took up her cause, Lydia discovered she's one of only 30 people in the world known to have a double DNA identity!

"I knew from watching TV that DNA tests are infallible," said Lydia, now 32. "But I knew the results were wrong. I knew I'd conceived and given birth to my children!"

Lydia's nightmare began when she was six months pregnant with her third child and she'd split up with her boyfriend Jamie – father of her son Jamie, 4, and daughter Jamesheny, 3.

When she applied for welfare benefits, a new state law required both parents to take DNA tests. They proved Jamie was the dad, but showed that Lydia and her children had different DNA!

"A court official told me: 'That scientifically proves you're not the mother!'" she recalled.

THE OFFICIAL ACCUSED Lydia of taking money to be a surrogate mom or even kidnapping the kids – and warned her that authorities could remove her children at any time!

After a second DNA test got the same result, Lydia headed back to court to keep her own kids. Lawyer after lawyer refused to take her case, saying DNA tests were never wrong.

Attorney Alan Tindell finally agreed to represent her, but only

'A court official told me: That scientifically proves you're not the mother'

after giving her the third degree. "I asked her all the tough questions she'd be asked in court: 'Are they really your kids or have you been a surrogate? Are they your sister's kids? Your brother's kids? Did you abduct them?'" he told The ENQUIRER.

"I've never seen a DNA test that was wrong, but I believed her story. So we needed to find out why her DNA tests were wrong."

AFTER WEEKS OF RESEARCH, he discovered the New England Journal of Medicine had documented an identical case. And researchers confirmed Lydia was a medical miracle – one of only 30 known people with a double DNA identity.

The incredibly rare condition called chimerism, which mea Lydia is her own twin.

Two fertilized eggs fused her mother's womb instead developing as twins. When th fused, so did the eggs' strands similar-but-distinct DNA.

As a result, samples from diff ent parts of Lydia's body can rev different DNA.

Armed with this medical inform tion, Lydia and Tindell went back court – and the judge dismissed t case.

"The ordeal of almost losing c children brought Jamie and me ba together. Our fourth child Jame was born a year ago," said Lydia, w now lives in Redmond, Wash.

"She doesn't have my DNA eith but I know I'm her mom!"

NE 22 December 11, 2006

Figure 2
A woman who gave birth to four children to whom she is related only as an aunt. Her husband, by contrast, is the genetic father of all four.

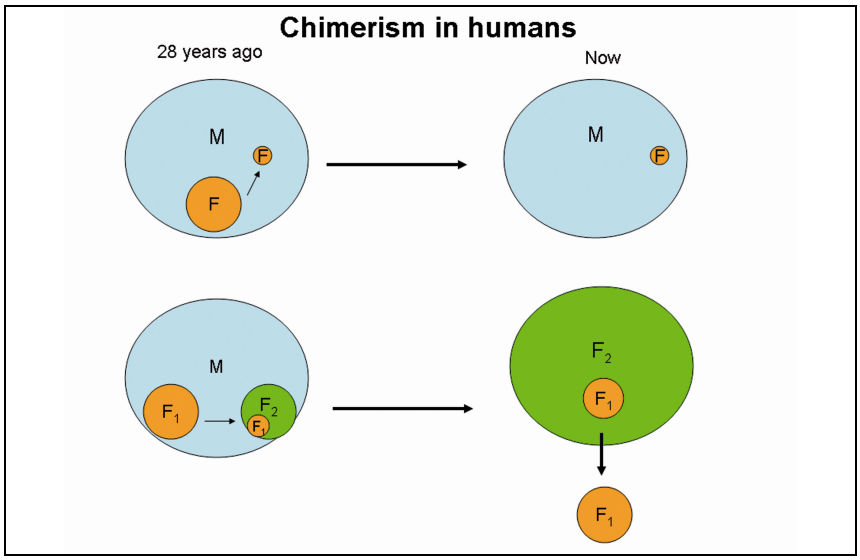

Figure 3
Bottom: a woman is pregnant with twin girls; the germ cells of one invade the ovaries of the other; the first dies, leaving a co-twin who is chimeric and later gives birth to her own nephews and nieces. Top: a fetus sends some of its cells into its mother and 28 years later the cells can still be found in the mother.

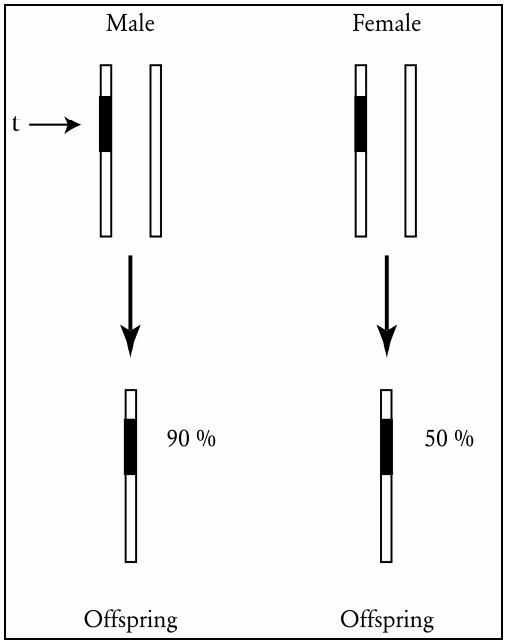

Figure 4
The *t*-haplotype drives in males only, showing 50 percent inheritance in females, but 90 percent in males (in a single mating). The *t* is roughly a third of the entire chromosome, that is, one percent of the entire genome. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 2.1, p. 22], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

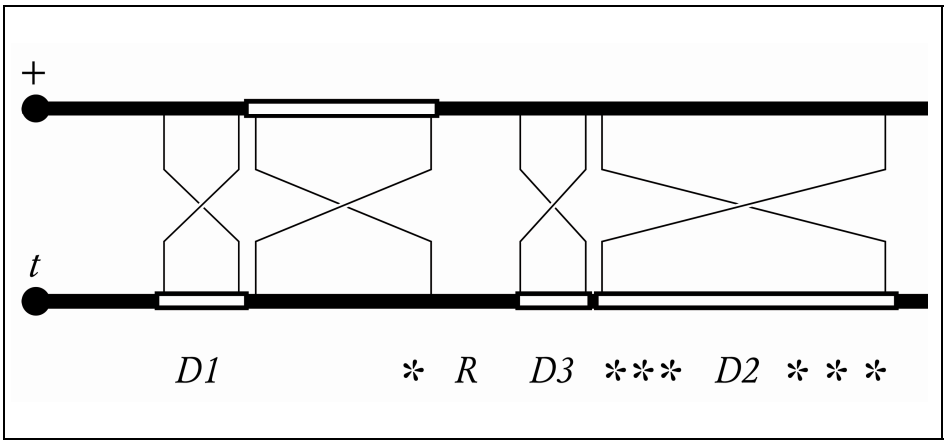

Figure 5
The structure of the *t*-haplotype: the *t* is covered by 4 non-overlapping inversions which cut recombination across the region from ~20% to 0.1%. A driver (D) is found in 3 of the inversions and there is probably one in the 4th as well. R is the resistance gene that protects the *t* from harming itself. * refer to lethals. Note that the second inversion occurred on the wild-type chromosome. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 2.2, p. 25], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

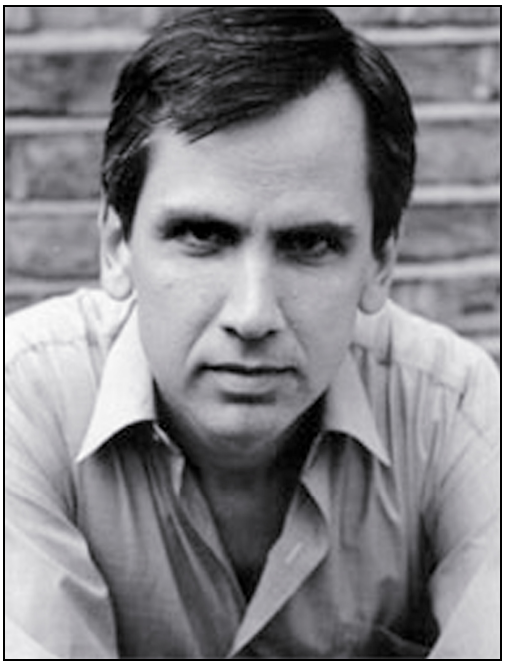

Figure 6
Austin Burt, Professor of Genetics, Imperial College, London. Burt has been especially creative in designing ways in which HEGs may be used to destroy human pests such as mosquitoes and their malarial guests.

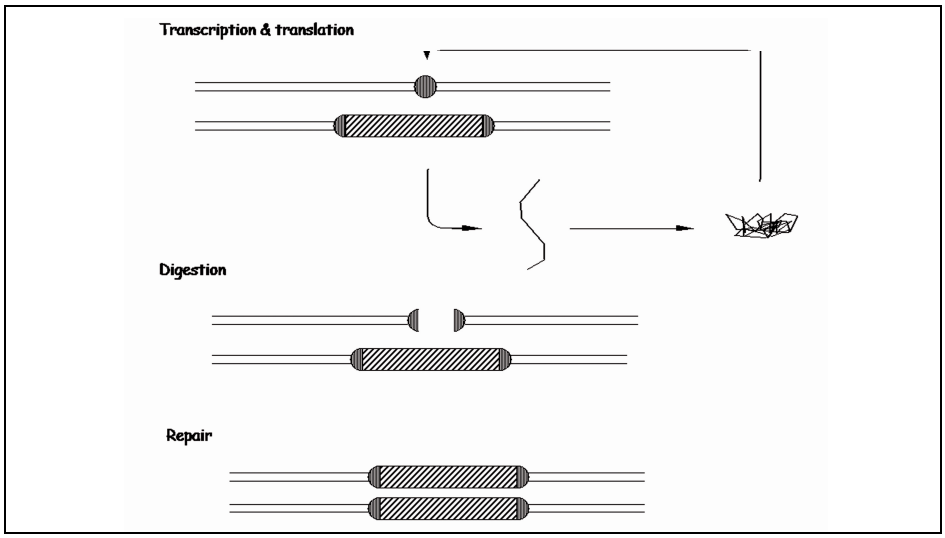

Figure 7
The mechanism of drive of homing endonuclease genes, as described in the text. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 6.3, p. 199], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

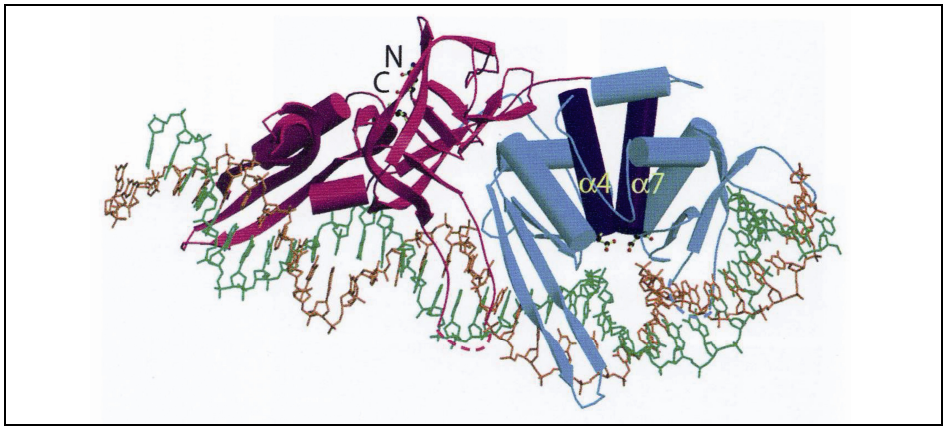

Figure 8
An actual picture of the *VDI* HEG protein attacking the double-stranded DNA. As you can see, the main part on the right looks likes a spider whose long legs are grabbing hold of the DNA and indeed pulling the DNA strand toward amino acids at the end of the α4 and α7 chains. These cause the chemical bonds to be broken in the double-stranded DNA creating the gap that the HEG then exploits to drive. Note the attached intein protein which will shortly separate. (Reprinted by permission of the Publisher from CRYSTAL STRUCTURE OF THE INTEIN HOMING ENDONUCLEASE PI-*SCE*I BOUND TO ITS RECOGNITION SEQUENCE by Carmen M. Moure, Frederick S. Gimble & Florante A. Quiocho [Fig. 2a, p. 765], Nature Structural Biology 9: 764–770, Copyright © 2002 by the Nature Publishing Group.)

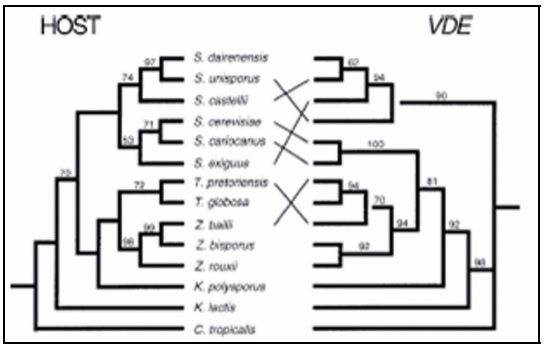

Figure 9
The phylogeny of the *VDI* HEG compared to its host yeast species. The two phylogenies fail to match up wherever a line is drawn between the host and *VDI* phylogenies. These are evidence of horizontal movements and at least half of the inheritance is explained by such horizontal transfer alone (Adapted from Koufopanou et al. 2002).

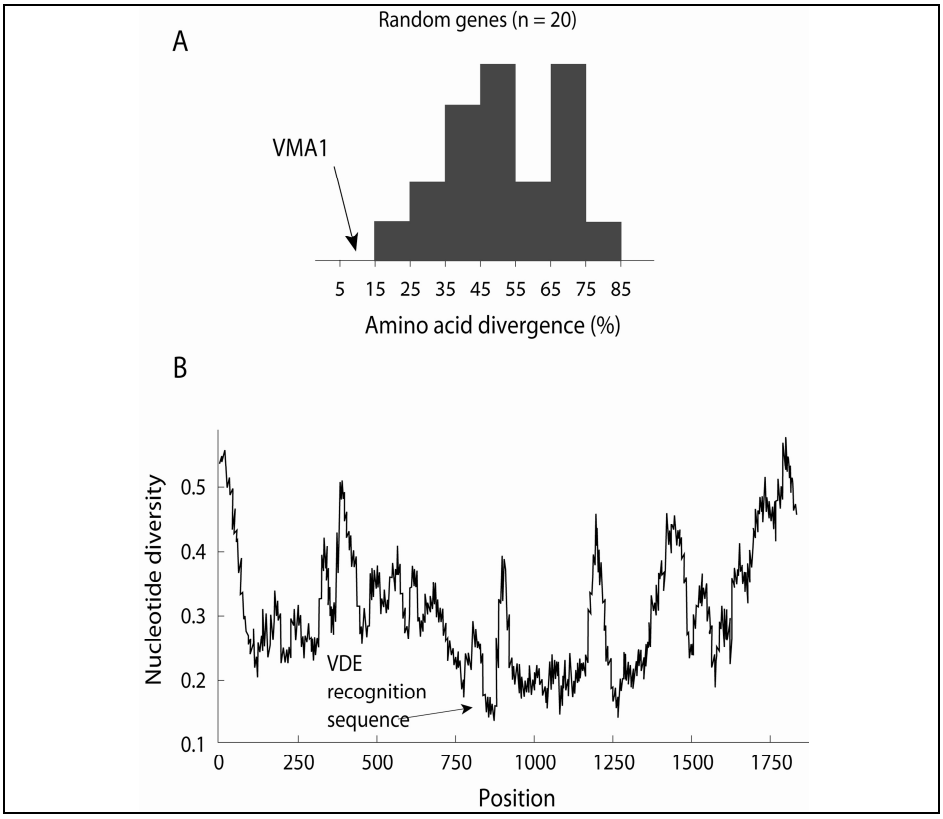

Figure 10
(a) The amount of the amino acid divergence of a random set of 20 genes across species of yeast with the degree of divergence of *VDI* shown by an arrow. (b) The degree of divergence within the gene targeted by *VDI* as a function of base pair position. Notice that the *VDI* attacks the least variable site (arrow) of a highly conservative gene. This is evidence of selection for horizontal gene transfer (Adapted from Koufopanou et al. 2002).

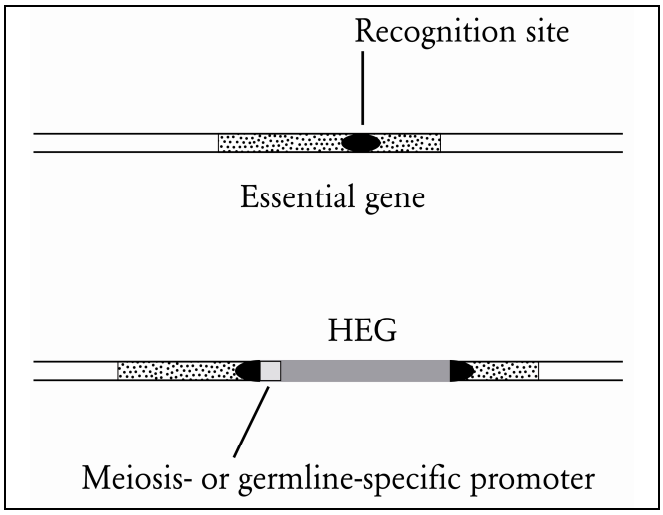

Figure 11
Austin Burt's scheme for using drive to tame a mosquito population. A recognition site is chosen inside an essential gene whose normal expression is dominant. And then a HEG is engineered to recognize this site. When it occupies a site it will disrupt functioning of the essential gene. If the gene is dominant the disruption of the phenotype will only occur when both copies have the inserted HEG. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 6.10, p. 219], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

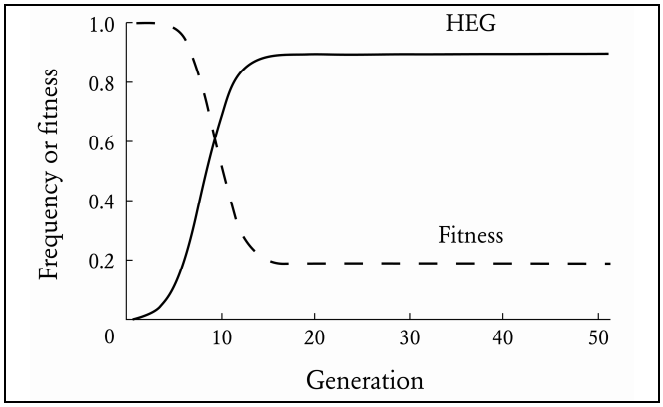

Figure 12
Time course of the invasion of an introduced driving HEG and its effect on its host population numbers. The solid line gives the frequency of the HEG, beginning at 1% and assuming 90% drive. The dashed line gives the size of the mosquito population. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 6.11, p. 220], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

Figure 13
Karin Mölling in her laboratory. She is an authority on viruses, with very creative thoughts on how to combat them.

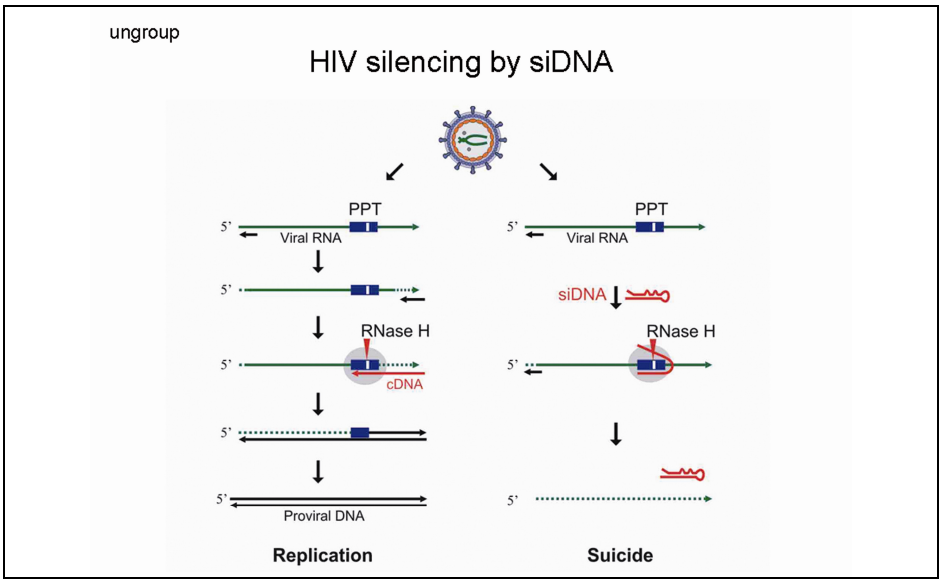

Figure 14
Normally (left hand arrow) RNase H cuts the RNA strand only after it has formed the complementary DNA strand but (right hand arrow) a siDNA can be engineered that binds to RNase H and causes it to cut the RNA strand prematurely, thus deleting the virus.

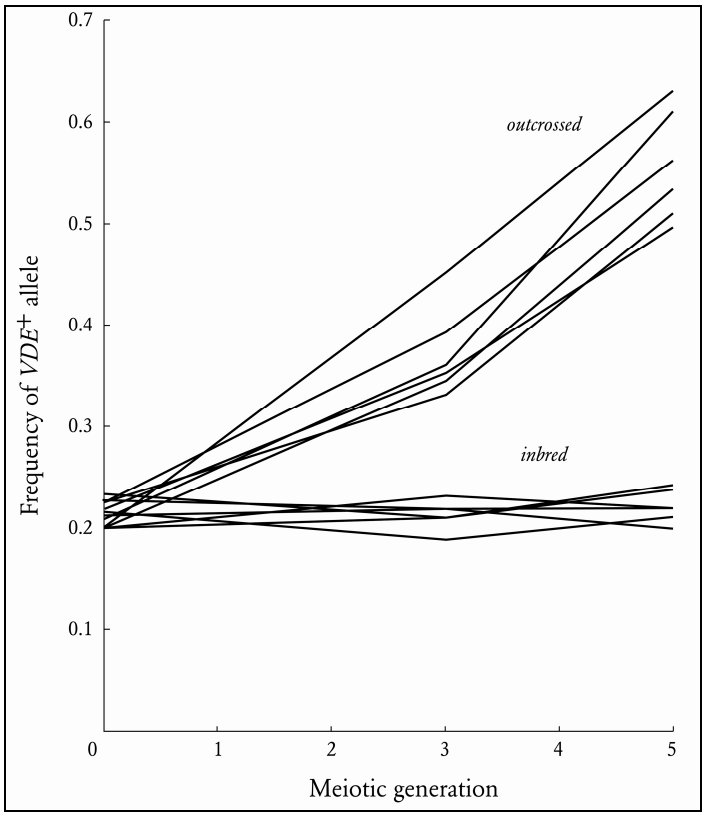

Figure 15
In yeast in the lab *VDE* spreads by outcrossing but fails to do so by inbreeding. Each line represents a separate experimental population. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 6.5, p. 203], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

B chromosomes and breeding system in British plants

Breeding system	No. species	% with B's
selfing	55	5.5
mixed	205	6.8
outcrossed	93	27.9
total	353	12.5

Figure 16
Frequency of B chromosomes is given in British flowering plants as a function of the breeding system of the plant. Bs predominate in outbred species (From Burt and Trivers 1998).

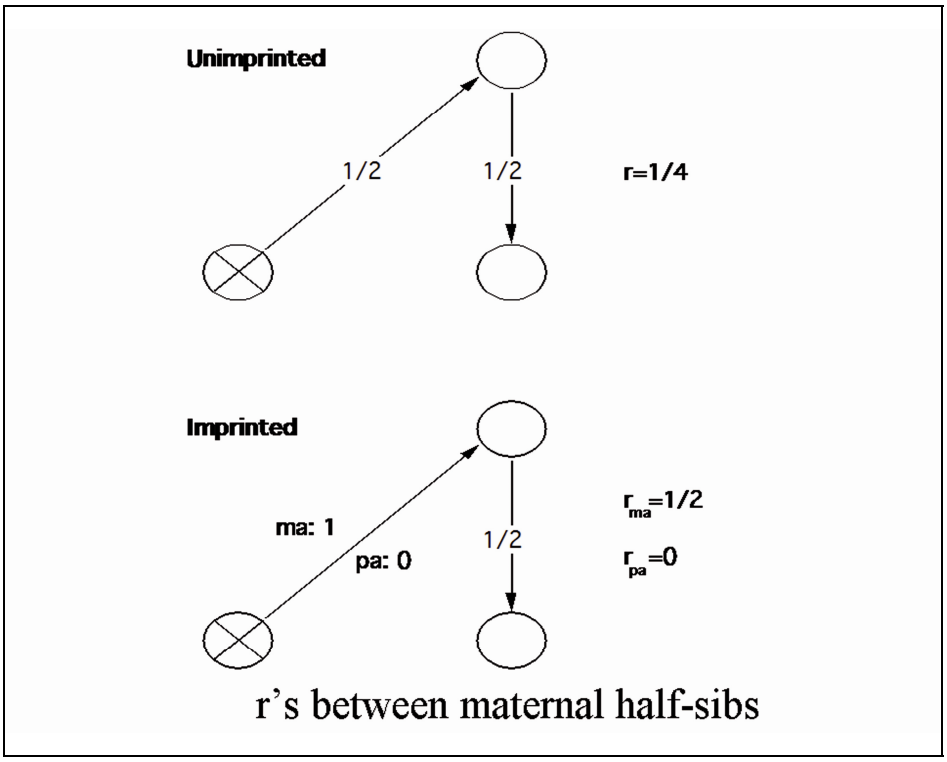

Figure 17
The first two (oppositely imprinted) genes discovered in mice. *Igf2* is paternally active and increases fetal growth while *Igf2r* is maternally active and has the opposite effect.

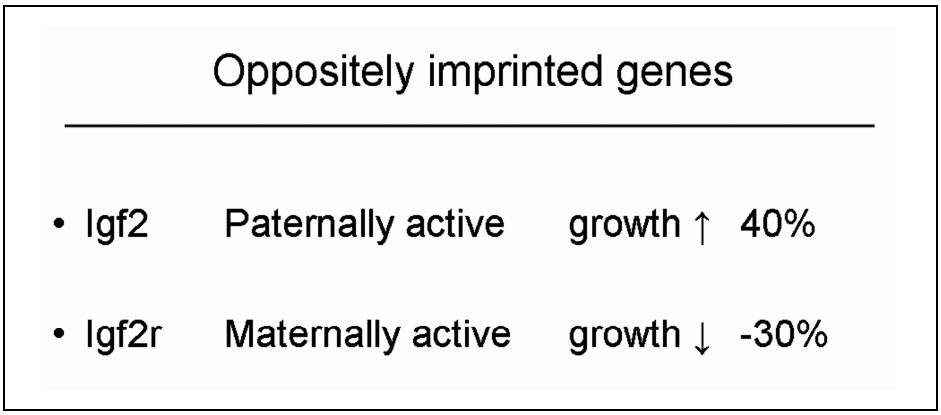

Figure 18
Degrees of relatedness (r) between two siblings related only through their mother for (top) unimprinted genes and (bottom) imprinted genes. See text.

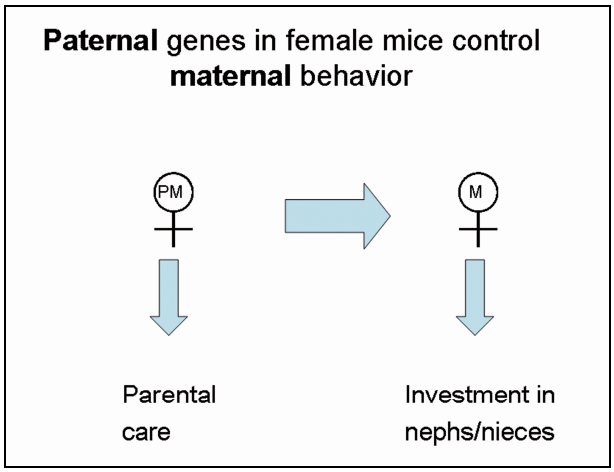

Figure 19
Maternal care in mice is controlled by at least two paternally active genes. Note that an individual female mouse is equally related to her offspring through her paternal (P) and her maternal (M) genes, but the latter are more related to female relatives nearby to whom they may be selected to divert some of the female's resources. Thus, the paternal genes in an adult female are more likely to stress personal reproduction – investment in own offspring – since they enjoy no increase in inclusive fitness by diverting resources to maternal relatives.

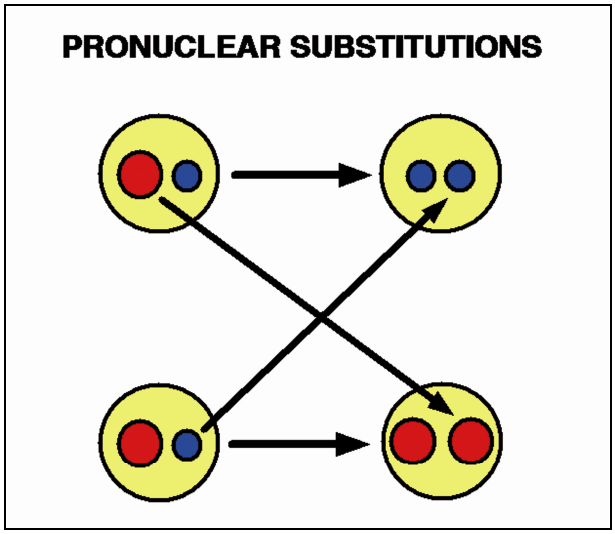

Figure 20
Pronuclear substitutions. By pipeting pronuclei from two sperm into one egg lacking a pronucleus and stimulating development, one can produce the beginning of a doubly paternal mouse. And adding a maternal pronucleus to an unfertilized egg produces a doubly maternal genome. Such extreme forms die early.

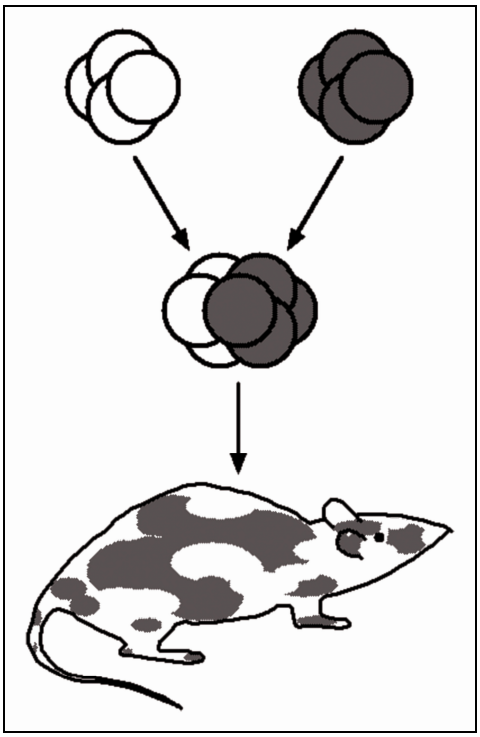

Figure 21
Mice chimeras consisting of a mixture of wild-type cells and either doubly-maternal or doubly-paternal cells can survive. They are created by allowing the two kinds of cells to mix very early in development (e.g. 4-cell stage embryos). (Image by courtesy of David Haig)

Contribution to brains of chimeric mice

	hypothalamus	neocortex
"two mums"	—	+ + +
"two dads"	+ + +	—

Figure 23
Chimeric mouse brains. Note that doubly maternal cells predominate in the neocortex of chimeric mice while doubly paternal ones predominate in the hypothalamus (Keverne et al. 1996). Since the neocortex is the largest section of the brain, this simple fact explains the brain weight plot in Figure 22.

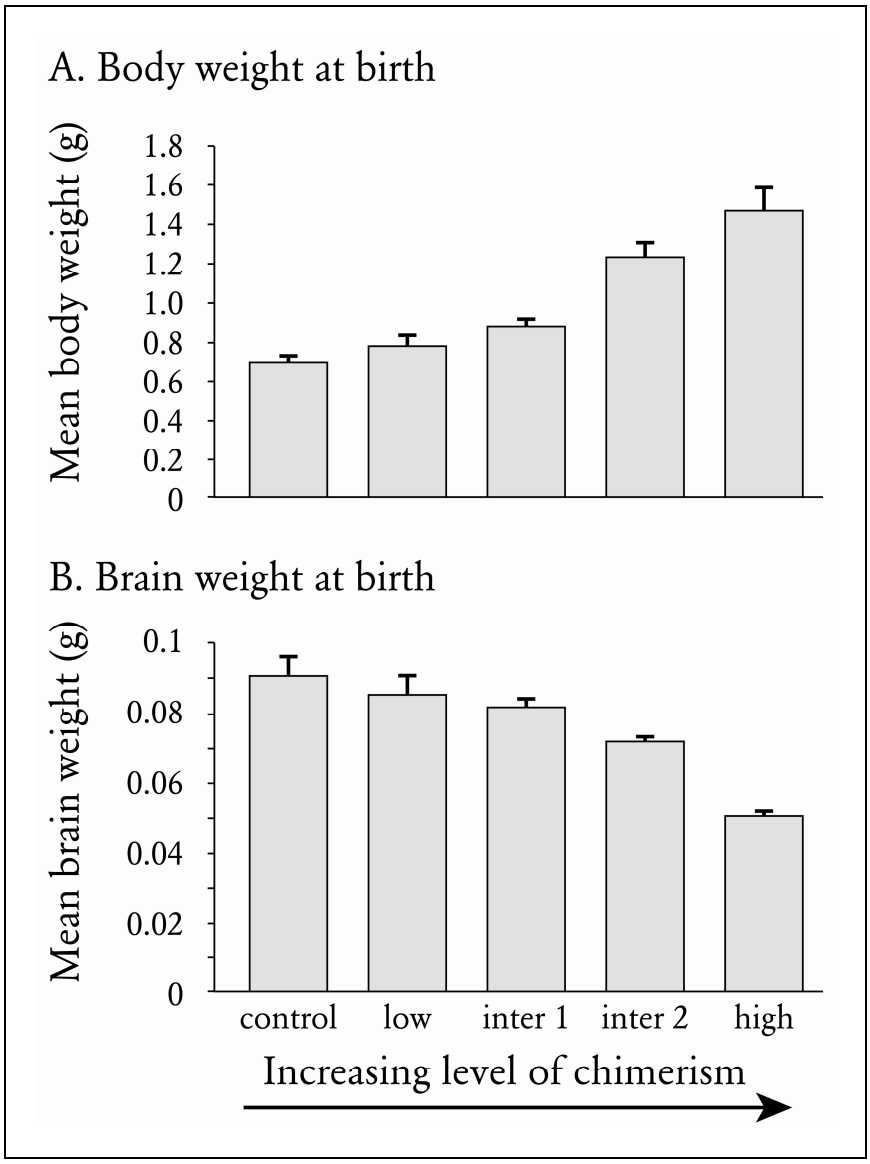

Figure 22
(A) Body weight at birth and (B) brain weight at birth are each plotted for mouse chimeras with increasing frequency of doubly paternal cells. Note that body size increases steadily while brain size decreases steadily. In other words relative brain size decreases even more rapidly. Highly doubly paternal mice barely have brain. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 4.4, p. 131], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

Figure 24
David Haig in his Harvard office. David is the only human being I know who literally splits every person he meets into a maternal and a paternal half and routinely splits any behavior (e.g. discounting functions) by how it may affect maternal and paternal genes differently.

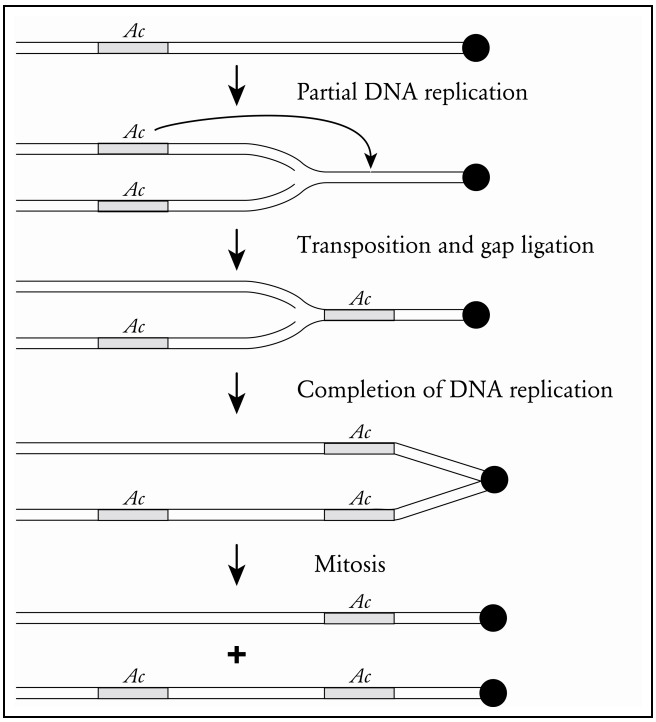

Figure 25
A simple DNA transposon. *Ac* waits for the replication fork to pass through it and it then takes this as a signal to leap ahead of the fork, landing mostly on the same chromosome, where it is then replicated a second time. This is 50% drive, going from an expected number of copies of 2 to 3. Note, as long as all elements remain intact, each can in principle repeat the trick into the indefinite future. Each transposon typically repeats the trick every 1000 generations or so. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 7.3, p. 234], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

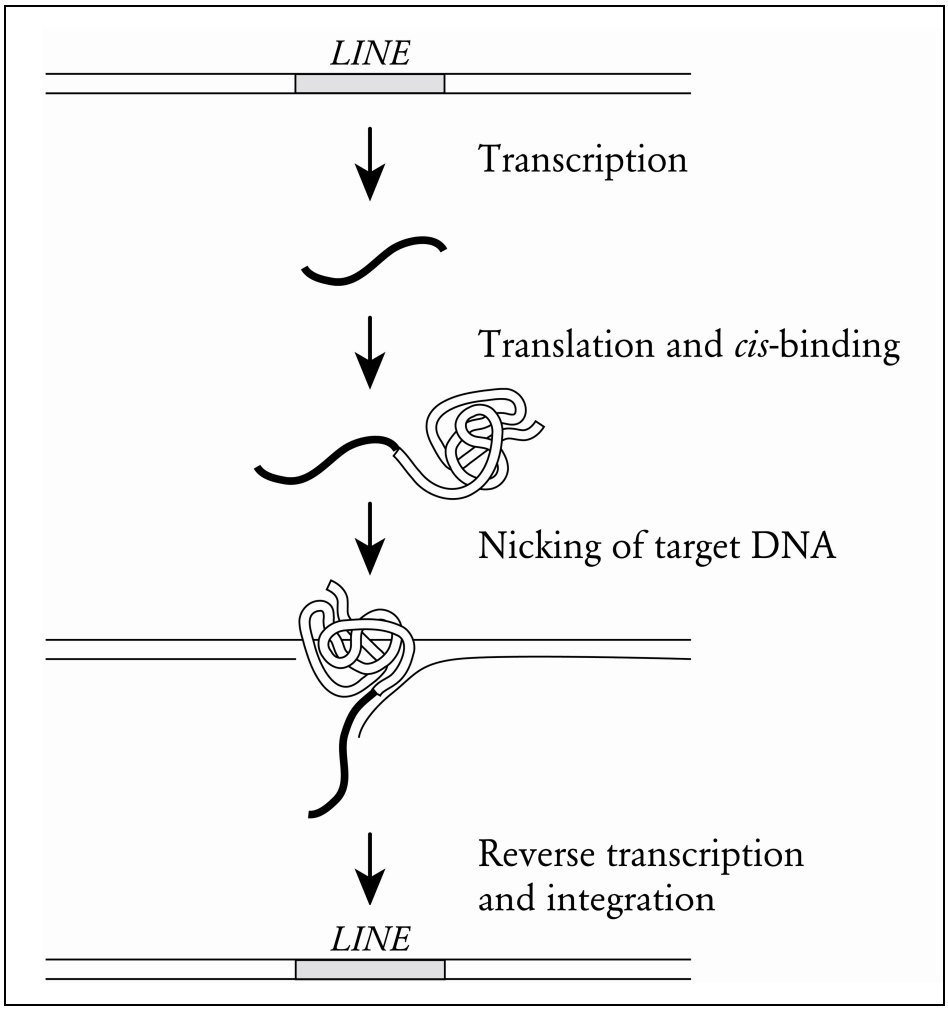

Figure 26
A simple RNA-mediated transposon (*LINE*). This trick consists of making an RNA strand which itself makes a protein to which it binds. Now the protein nicks the genome at a new located and reverse transcriptase translates the RNA back into DNA. The element has doubled in number. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 7.4, p. 236], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

Approximate transposable element composition of the human genome

	No. of Inserts	% of Genome Total	% of Genome Last 75my*
•DNA transposons	400,000	3	1
•LINEs	1,000,000	21	8
•SINEs	2,000,000	14	11
•LTR retroelements	600,000	9	4
•Total	4,000,000	46	24

•* Transposable element inserts acquired in the last 75my (i.e., not shared with mice).
•From Lander et al. (2001) and Waterston et al. (2002).

Figure 27
Percentage of the human genome made up of various transposable element fossils (no longer active). Rough total is 50% and this must be an underestimate.

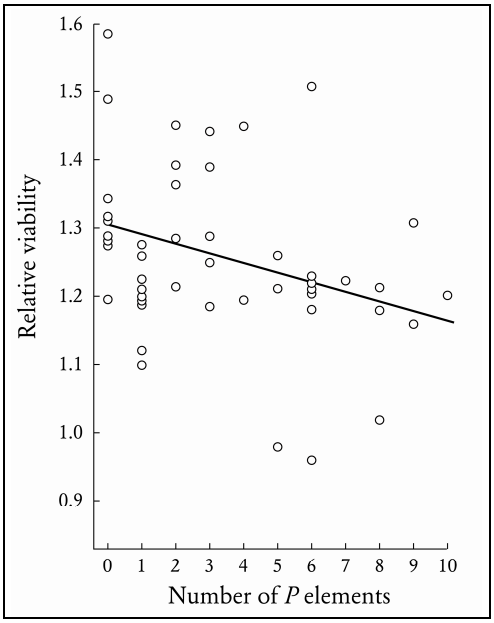

Figure 28
Survival as a function of number of *P*-element inserts on the *X*-chromosome of *Drosophila* males–thus every insert will be expressed in the phenotype if it disrupts a gene. (Reprinted by permission of the Publisher from GENES IN CONFLICT: THE BIOLOGY OF SELFISH GENETIC ELEMENTS by Austin Burt and Robert Trivers [Fig. 7.8, p. 248], Cambridge, Mass,: The Belknap Press of Harvard University Press, Copyright © 2006 by the President and Fellows of Harvard College.)

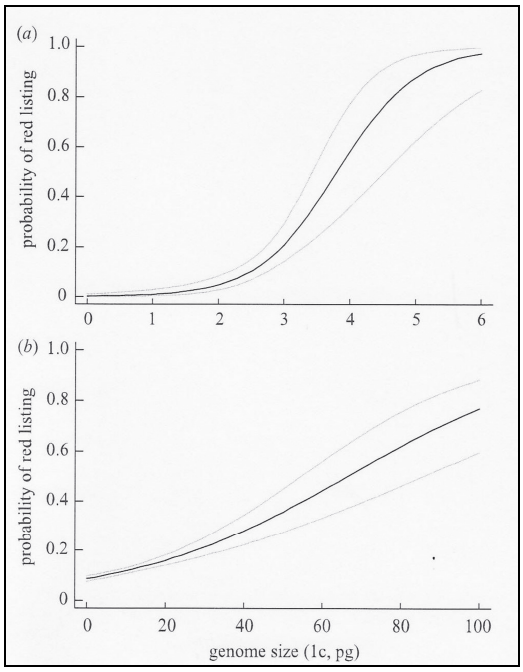

Figure 29
Probability of a species being Red-listed for danger of extinction in (a) reptiles and (b) plants. Note that variation in genome size in plants occurs over two orders of magnitude and there is a strong tendency for larger genomes to put the species at greater risk of extinction. Indeed, on average red-listed species have genomes twice as large as species not at risk. A similar effect is seen in reptiles (but not, for example, mammals or fish). (From A. E. Vinogradov: Genome size and extinction risk in vertebrates, Proceedings. Biological Sciences / The Royal Society, 2004, 271: 1701–1705, Fig. 5, p. 1705. Reprinted by permission of the Royal Society, London.)

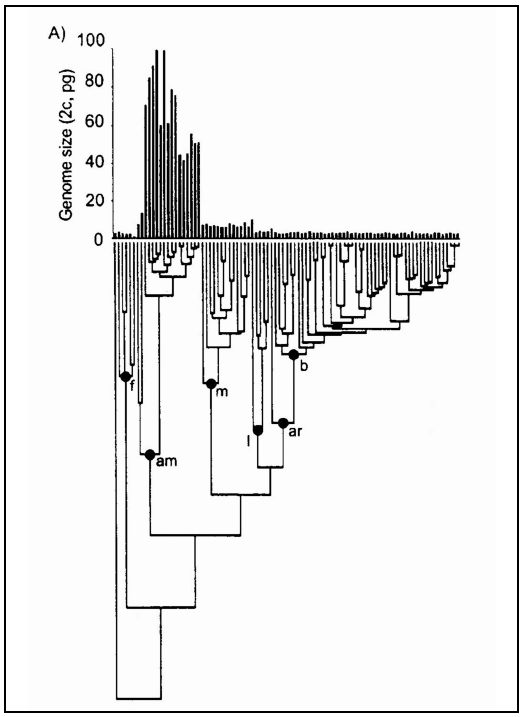

Figure 30

Genome sizes are shown for vertebrates (especially birds). The phylogeny is below the axis and genome sizes are given in picograms per diploid genome. (Reprinted by permission of the Publisher from THE EVOLUTIONARY DYNAMICS OF INTRON SIZE, GENOME SIZE, AND PHYSIOLOGICAL CORRELATES IN ARCHOSAURS by E. Waltari and S. V. Edwards [Fig. 2, p. 545], American Naturalist 160: 539–552, Copyright © 2002, The University of Chicago Press.)

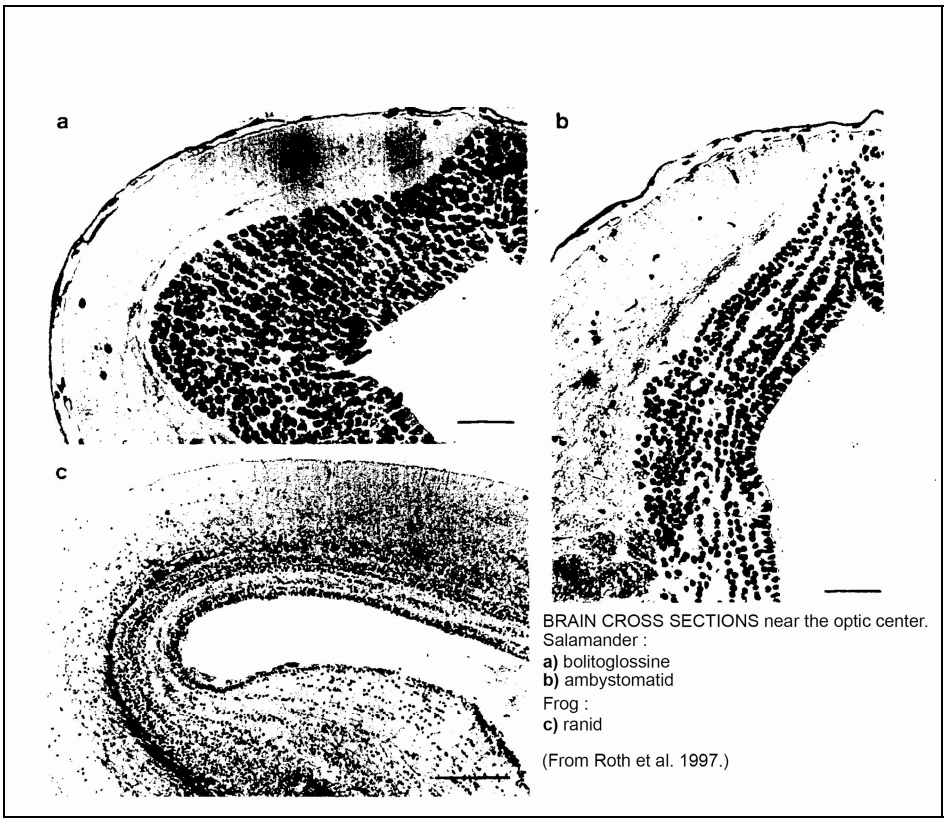

Figure 31
Cross sections of the brain near the optic center for salamanders: (a) bolittoglossine, (b) ambystomatid and a frog: (c) ranid. Note that the nervous system is least complex for the large-genomed ambystomatid salamander, more complex for the genome intermediate in size (bolittoglosine) and most complex in the species with the smallest genome, a ranid frog (From G. Roth, K. C. Nishikawa, and D. B. Wake (1997): Genome size, secondary simplification, and the evolution of the brain size in salamanders [Fig. 1, p. 53], Brain Behav. Evol. 50: 50–59. Reprinted by permission of the S. Karger AG, Medical and Scientific Publishers, Basel).

Figure 32
Ernst Mayr lecturing late in life – “the meaning of the mechanism”.