

[Print this page](#)

## A Gene For Nothing

10.01.1997

### **One to make you happy, one to make you sad, one to make you mad--is that really the way your genes work?**

by Robert Sapolsky

Well, these last six months have been an exciting time for the sheep named Dolly, ever since it was revealed that she was the first mammal cloned from adult cells. There was the night she spent in the Lincoln bedroom and the photo op with Al Gore; the triumphant ticker-tape parade down Broadway, the billboard ads for Guess Genes. Throughout the media circus, Dolly has been poised, patient, cordial, and even-tempered--the epitome of what we look for in a celebrity and role model. But despite her charm, people keep saying mean things about Dolly. Heads of state, religious leaders, and editorialists fall over themselves in calling her an aberration of nature and an insult to the sacred biological wonder of reproduction. They thunder about the anathema of even considering applying to humans the technology that spawned her.

What's everyone so upset about? Why is cloning so disturbing? Clearly, it's not the potential for droves of clones running around with the exact same renal filtration rate that has everyone up in arms. It's probably not even the threat of winding up with a bunch of clones who look identical, creepy though that would be. No, the real horror is the prospect of having multiple copies of a single brain, with the same neurons and the same genes directing those neurons, one multibodied consciousness among the clones, an army of photocopies of the same soul, all thinking, feeling, and acting identically.

Fortunately, that can't happen, as people have known ever since scientists discovered identical twins. Such individuals constitute genetic clones, just like Dolly and her mother--the sheep from which the original cell was taken. Despite all those breathless stories about identical twins separated at birth who flush the toilet before using it, twins are not melded in mind, do not behave identically. For example, if an identical twin is schizophrenic, the sibling, with the identical schizophrenia gene(s), has only about a 50 percent chance of having the disease.

A similar finding comes from a fascinating experiment by Dan Weinberger of the National Institute of Mental Health. Give identical twins a puzzle to solve and they might come up with closer answers than one would expect from a pair of strangers. While they're working on the puzzle, however, hook the twins up to a pet scanner, a brain-imaging instrument that visualizes metabolic demands in different regions of the brain. You'll find the pattern of activation in the pair differing considerably, despite the similarity of their solutions. Or use an mri to get some detailed pictures of the brains of identical twins and start measuring stuff obsessively--the length of this part, the width of that, the volume of another region, and the surface area of the cortex--and those identical twins with their identical genes never have identical brains. Every measure differs.

The careful editorialists have made this point. Nonetheless, that business about identical genes producing identical brains tugs at a lot of people. Gene-behavior stories are constantly getting propelled to the front pages of newspapers. One popped up shortly before Dolly, when a team of researchers reported that a single gene, called fru, determines the sexual behavior of male fruit flies. Courtship, opening lines, foreplay, who they come on to--the works. Mutate that gene and--get this--you can even change the sexual orientation of the fly. What made the story front-page news, of course, wasn't our insatiable fly voyeurism. Could our sexual behaviors be determined by a single gene as well? every article asked. And a bit earlier, there was the hubbub about the isolation of a gene related to anxiety in humans, and shortly before that, a gene related to novelty-seeking behavior, and a while before that, a gene whose mutation in one family was associated with violent antisocial behavior, and before that. . .

Why do these stories command attention? For many, genes and the DNA they contain represent the holy grail of biology, the code of codes (two phrases often used in lay discussions of genetics). The worship at the altar of the gene rests on two assumptions. The first concerns the autonomy of genetic regulation: it is the notion that biological information begins with genes--dna is the commander, the epicenter from which biology emanates. Nobody tells a gene what to do; it's always the other way around. The second assumption is that when genes give a command, biological systems listen. Genes, the story goes, instruct your cells as to their structure and function. And when those cells are neurons, their functions include thought, feelings, and behavior. Thus, the gene worshipers believe, we are finally identifying the biological factors that make us do what we do.

A typical example of the code-of-codes view recently appeared in a lead New Yorker article by Louis Menand, an English professor at the City University of New York. Menand ruminates on anxiety genes, when one little gene is firing off a signal to bite your fingernails (there's that first assumption--autonomous genes firing off whenever some notion pops into their heads). He asks himself how we can reconcile societal, economic, and psychological explanations of behavior with those ironclad genes. The view that behavior is determined by an inherited genetic package (there's the second assumption--genes as irresistible commanders) is not easily reconciled with the view that behavior is determined by the kinds of movies a person watches. And what is the solution? It is like having the Greek gods and the Inca gods occupying the same pantheon. Somebody's got to go.

In other words, if you buy into the notion of genes firing off and determining our behaviors, such modern scientific findings are simply incompatible with the environment having an influence. Something's gotta go.

Now, I'm not sure what sort of genetics they teach in Menand's English department, but the something's-gotta-go loggerhead is what most behavioral biologists have been trying to unteach for decades, apparently with limited success. Which is why it's worth another try.

Okay. You've got nature--neurons, brain chemicals, hormones, and of course, at the bottom of the cereal box, genes. And then there's nurture, all those environmental breezes gusting about. Again and again, behavioral biologists insist that you can't talk meaningfully about nature or nurture, only about their interaction. But somehow people can't seem to keep that thought in their heads. Instead, whenever a new gene is trotted out that determines a behavior by firing off, they see environmental influences as the irrelevant something that has to go. Soon poor, sweet Dolly is a menace to our autonomy as individuals, and genes are understood to control who you go to bed with and whether you feel anxious about it.

Let's try to undo the notion of genes as neurobiological and behavioral destiny by examining those two assumptions, beginning with the second one--that cells, including those in our heads, obey genetic commands. What exactly do genes do? A gene, a stretch of DNA, does not produce a behavior. A gene does not produce an emotion, or even a fleeting thought. It produces a protein. Each gene is a specific DNA sequence that codes for a specific protein. Some of these proteins certainly have lots to do with behavior and feelings and thoughts; proteins include some hormones (which carry messages between cells) and neurotransmitters (which carry messages between nerve cells); they also include receptors that receive hormonal and neurotransmitter messages, the enzymes that synthesize and degrade those messengers, many of the intracellular messengers triggered by those hormones, and so on. All those proteins are vital for a brain to do its business. But only very rarely do things like hormones and neurotransmitters cause a behavior to happen. Instead they produce tendencies to respond to the environment in certain ways.

To illustrate this critical point, let's consider anxiety. When an organism is confronted with a threat, it typically becomes vigilant, searches for information about the nature of the threat, and struggles to find an effective coping response. Once it receives a signal indicating safety--the lion has been evaded, the traffic cop buys the explanation and doesn't issue a ticket--the organism can relax. But that's not what happens with an anxious individual. Instead this person will skitter frantically among coping responses, abruptly shifting from one to another without checking whether anything has worked. He may have a hard time detecting the safety signal and knowing when to stop his restless vigilance. Moreover, the world presents a lot of triggers that not everyone reacts to. For the anxious individual, the threshold is lower, so that the mere sight of a police car in the rearview mirror can provoke the same storm of uneasiness as actually being stopped. By definition, anxiety makes little sense outside the context of what the environment is doing to an individual. In that framework, the brain chemicals and genes relevant to anxiety don't make you anxious. They make you more responsive to anxiety-provoking situations, make it harder to detect safety signals.

The same theme continues in other behaviors as well. The exciting (made-of-protein) receptor that apparently has to do with novelty-seeking behavior doesn't actually make you seek novelty. It makes you more pleasurably excited than folks without that receptor variant get when you happen to encounter a novel environment. And those (genetically influenced) neurochemical abnormalities of depression don't make you depressed. They make you more vulnerable to stressors in the environment, to deciding that you are helpless even when you're not.

One might retort that in the long run we are all exposed to anxiety-provoking circumstances, all exposed to the depressing world around us. If we are all exposed to those same environmental factors but only the people who are genetically prone to depression get depressed, that is a pretty powerful vote for genes. In that scenario, the genes don't cause things, they just make you more sensitive to the environment argument becomes empty and semantic.

The problems here, however, are twofold. First, a substantial minority of people with a genetic legacy of depression do not get depressed, and not everyone who has a major depression has a genetic legacy for it. Genetic status is not all that

predictive by itself. Second, we share the same environments only on a very superficial level. For example, the incidence of depression (and its probable biological underpinnings) seem to be roughly equal throughout the world. However, geriatric depression is epidemic in our society and far less prevalent in traditional societies in the developing world. Why? Different societies produce remarkably different social environments, in which old age can mean being a powerful village elder or an infantilized has-been put out to a shuffleboard pasture.

The environmental differences can be more subtle. Periods of psychological stress involving loss of control and predictability during childhood may well predispose one toward adult depression. Two children may have had similar childhood lessons in there's bad things out there that I can't control--both may have seen their parents divorce, lost a grandparent, tearfully buried a pet in the backyard, faced the endless menacing of a bully. Yet the temporal pattern of their experience is unlikely to be identical, and the child who experiences all those stressors over a one-year period instead of over six years is far more likely to come with the cognitive distortion, There's bad things out there that I can't control and, in fact, I can't control anything, that sets you up for depression. The biological factors that genes code for in the nervous system typically don't determine behavior. Instead they affect how you respond to often very subtle influences in the environment. There are genetic vulnerabilities, tendencies, predispositions--but rarely genetic inevitabilities.

Now let's go back to that first assumption about behavioral genetics--that genes always have minds of their own. It takes just two startling facts about the structure of genes to blow this one out of the water.

A chromosome is made of DNA, a vastly long string of it, a long sequence of letters coding for genetic information. People used to think that Gene 1 would comprise the first eleventy letters of the DNA message. A special letter sequence would signal the end of that gene, the next eleventy and a half letters would code for Gene 2, and so on, through tens of thousands of genes. Gene 1 might specify the construction of insulin in your pancreas; Gene 2 might specify protein pigments that give eyes their color; and Gene 3, active in neurons, might make you aggressive. Ah, caught you: might make you more sensitive to aggression-provoking stimuli in the environment. Different people have different versions of Genes 1, 2, and 3, some of which work better than others. An army of biochemicals do the scut work, transcribing the genes, reading the DNA sequences, and following the instructions they contain for constructing the appropriate proteins.

As it turns out, that's not really how things work. Instead of one gene coming immediately after another, with the entire string of DNA devoted to coding for different proteins, there are long stretches of DNA that don't get transcribed. Sometimes those stretches even split up a gene into subsections. Some of the nontranscribed, noncoding DNA doesn't seem to do anything. It may have some function that we don't yet understand, or it may have none at all. But some of the noncoding DNA does something very interesting indeed. It's the instruction manual for how and when to activate genes. These stretches have many names--regulatory elements, promoters, responsive elements. Various biochemical messengers may bind to each of them, altering the activity of the gene immediately downstream-- immediately following it in the string of DNA.

Far from being autonomous sources of information, then, genes must obey other factors that regulate when and how they function. Very often, those factors are environmental. For example, suppose something stressful happens to a primate. A drought, say, forces to it forage miles each day for food. As a result, the animal secretes a stress hormone, cortisol, from its adrenals. Cortisol molecules enter fat cells and bind to cortisol receptors. These hormone-receptor complexes find their way to the DNA and bind to a regulatory stretch of DNA. Whereupon a gene downstream is activated, which produces a protein, which indirectly inhibits that fat cell from storing fat. It's a logical thing to do--while starving and walking the grasslands in search of a meal, the primate needs fat to fuel muscles, not to laze around in fat cells.

In effect, regulatory elements introduce the possibility of environmentally modulated if-then clauses. If the environment is tough and you're working hard to find food, then make use of your genes to divert energy to exercising muscles. The environment, of course, doesn't mean just the weather. The biology is essentially the same if a human refugee travels miles from home with insufficient food because of civil strife. The behavior of one human can change the pattern of gene activity in another.

Let's look at a fancier example of how environmental factors control the regulatory elements of DNA. Suppose that Gene 4037 (not its real name--it has one, but I'll spare you the jargon), when left to its own devices, is transcriptionally active, generating its protein. However, as long as a particular messenger binds to a regulatory element that comes just before 4037 in the DNA string, Gene 4037 shuts down. Fine. Now suppose that inhibitory messenger happens to be very sensitive to temperature. In fact, if the cell gets hot, the messenger goes to pieces and comes floating off the regulatory element. Freed from the inhibitory regulation, Gene 4037 will suddenly become active. Maybe it's a gene that works in the kidney and codes for a protein relevant to water retention. Boring--another metabolic story, this one having to do with how a warm environment triggers metabolic adaptations that stave off dehydration. But suppose, instead, Gene 4037 codes

for an array of proteins that have something to do with sexual behavior. What have you just invented? Seasonal mating. Winter is waning, each day gets a little warmer, and in relevant cells in the brain, pituitary, or gonads, genes like 4037 are gradually becoming active. Finally some threshold is passed and, wham, everyone starts rutting and ovulating, snorting and pawing at the ground, and generally carrying on. (Actually, in most seasonal matters, the environmental signal for mating is the amount of daily light exposure, or the days are getting longer, rather than temperature, or the days are getting warmer. But the principle is the same.)

Here's a final, elegant example. Every cell in your body has a distinctive protein signature that marks it as yours. These major histocompatibility proteins allow your immune system to tell the difference between you and some invading bacterium—that's why your body will reject a transplanted organ with a very different signature. When those signature proteins get into a mouse's urine, they help make its odor distinct. For a rodent, that's important stuff. Design receptors in olfactory cells in a rodent's nose that can distinguish signature odorant proteins similar to its own from totally novel ones. The greater the similarity, the tighter the protein will fit into the receptor. What have you just invented? A way to distinguish between the smells of relatives and strangers—something rodents do effortlessly.

Keep tinkering with this science project. Now couple those olfactory receptors to a cascade of chemical messengers inside the cell, one messenger triggering the next until you get to the DNA's regulatory elements. What might you want to construct? How about: If an olfactory receptor binds an odorant indicating the presence of a relative, then trigger a cascade that ultimately inhibits the activity of genes related to reproduction. You've just invented a mechanism by which animals could avoid mating with close relatives. Or you can construct a different cascade: if an olfactory receptor binds an odorant indicating a relative, then inhibit genes that are normally active and that regulate the synthesis of testosterone. There you have a means by which rodents get bristly and aggressive when a strange male stinks up their burrow but not when the scent belongs to their kid brother.

In each of these examples you can begin to see the logic, an elegance that teams of engineers couldn't do much to improve. And now for the two facts about this regulation of genes that will dramatically change your view of them. First, when it comes to mammals, by the best estimates available, more than 95 percent of DNA is noncoding. Ninety-five percent. Sure, a lot of it may have no function, but your average gene comes with a huge instruction manual for how to operate it, and the operator is very often environmental. With a percentage like that, if you think about genes and behavior, you have to think about how the environment regulates genes and behavior.

The second fact involves genetic variation between individuals. A gene's DNA sequence often varies from person to person, which often translates into proteins that differ in how well they do their job. This is the grist for natural selection: Which is the most adaptive version of some (genetically influenced) trait? Given that evolutionary change occurs at the level of DNA, survival of the fittest really means reproduction of individuals whose DNA sequences make for the most adaptive collection of proteins. But—here's that startling second fact—when you examine variability in DNA sequences among individuals, the noncoding regions of DNA are considerably more variable than are the regions that code for genes. Okay, a lot of that variability is attributable to DNA that doesn't do much and so is free to drift genetically over time without consequence. But there seems to be a considerable amount of variability in regulatory regions as well.

What does this mean? By now, I hope, we've gotten past genes determine behavior to genes modulate how one responds to the environment. The business about 95 percent of DNA being noncoding should send us even further, to genes can be convenient tools used by environmental factors to influence behavior. And that second fact about variability in noncoding regions means that it's less accurate to think evolution is about natural selection for different assemblages of genes than it is to think evolution is about natural selection for different sensitivities and responses to environmental influences.

Sure, some behaviors are overwhelmingly under genetic control. Just consider all those mutant flies hopping into the sack with insects their parents disapprove of. And some mammalian behaviors, even human ones, are probably pretty heavily under genetic regulation as well. These are likely to code for behaviors that must be performed by everyone in much the same way for genes to be passed on. For example, all male primates have to go about the genetically based behavior of pelvic thrusting in fairly similar ways if they plan to reproduce successfully. But by the time you get to courtship, or emotions, or creativity, or mental illness, or any complex aspect of our lives, the intertwining of biological and environmental components utterly defeats any attempt to place them into separate categories, let alone to then decide that one of them has got to go.

I'm a bit hesitant to reveal the most telling example of how individuals with identical genes can nonetheless come up with very different behaviors, as I have it thirdhand through the science grapevine, and I'll probably get some of the details wrong. But what the hell, it's such an interesting finding. It concerns the very extensive opinion poll that was carried out

among sheep throughout the British Isles. Apparently, the researchers managed to get data from both Dolly and her gene-donor mother. So get a load of this bombshell: Dolly's mother voted Tory, listed the Queen Mum as her favorite royal, worried about mad cow disease (Is it good or bad for the sheep?), enjoyed Gilbert and Sullivan, and endorsed the statement, Behavior? It's all nature. And Dolly? Votes Green Party, thinks Harry and William are the cutest, worries about the environment, listens to the Spice Girls, and endorsed the statement, Behavior? Nature. Or nurture. Whatever. You see, there's more to behavior than just genes.