Notes about this pitch letter (David Dobbs, Oct 23, 2010):

• I've snipped a few things I don't want out and about yet — material I'm still working up, that sort of thing.

• I usually would not send a pitch letter this long, but I'd talked the idea over extensively with the editor, and as that got us past the "Is this worth a look" stage, he wanted the long version so the answers to inevitable questions were included. I usually limit my initial pitch letters to no more than 3 paragraphs, and offer to provide more detail if needed. Few editors would read a pitch letter this long if it just showed up in their inbox.

The pitch, sent via email to *Atlantic* editor Don Peck, June 3, 2010:

Dear Don,

Below is the pitch, revised to reflect our talk last week as well as a few more tidbits I found. Let me know if you need anything else.

Thanks again, and hope to talk soon.

Best,

David Dobbs

[phone #]

http://neuronculture.com

Dandelion Kids and Orchid Children

How vulnerability is responsiveness, danger opportunity, and an apparent weakness — genetically conferred sensitivity to environment — may be the secret to human (and humankind's) success

This story looks at a radically new interpretation of one of the most important lines of psychiatric and personality research of the last decade or so: the identification of genetic variations that, in combination with stress or troubled times (especially early in life), make people more "vulnerable" to certain mood, psychiatric, or personality disorders.

The model being revised is fairly well known: Over the past decade or two, researchers have discovered a half-dozen or so key behavioral genes that have certain versions (or alleles) that increase your susceptibility to depression, ADHD, sociopathic or violent behavior, anxiety, or other problems if — and only if — you also suffer a difficult childhood or particularly trying experiences later. This hypothesis has already transformed our conception of psychiatric illness and many dysfunctional behaviors: they are no longer considered the

result of either nature or nurture but the product of "gene-environment interactions." Call it the "vulnerability" hypothesis: Your genes don't doom you to these disorders, but "bad" versions of certain genes render you more prone to them if life treats you ill.

Now rising from this vulnerability hypothesis is a novel idea that builds on this model even as it turns it inside out. This new view sees these same genetic predispositions not as unidirectional vulnerabilities (opening only one pathway, down) but as bidirectional leveraged bets — a heightened responsiveness to early experience that creates generally dysfunctional behavior in those raised in rough environments but heightened function and performance in those raised in highly nurturing environments.

This idea is new enough to today's biological psychiatry that it's still in search of a name, with the leading candidates being "differential susceptibility," "heightened responsiveness," and "biological sensitivity to context," or BSC. Yet its model is recognized in an old Swedish distinction between "dandelion children" and "orchid children": dandelion kids (that is, "normal" or "healthy" children with "resilient" or "protective" genes) do pretty well almost anywhere, whether an abandoned lot or a well-tended garden. Orchid children, meanwhile — those with the "vulnerability" gene versions — wilt if maltreated but flourish if pampered in a greenhouse.

At first glance this model — call it the orchid hypothesis — may seem a simple amendment to the vulnerability hypothesis: it merely adds that environment and experience can steer a person up instead of down. Yet it's a complete reconception. It transforms biological foundations that science currently sees as unfortunate, accidental vulnerabilities (poor Jim, got the "bad" allele) into leveraged bets — gambles that create a sort of diversified-portfolio approach to evolutionary investment, with selection favoring parents who produce both dandelions and orchids. This emphasis on variable, bidirectional responsiveness revises our view not just of mental illness and behavioral dysfunction but of human nature, human evolution, even the roots of humanity's spectacular success.

Vulnerability as flexibility

The evidence for this orchid hypothesis has emerged over the past decade or so, and especially the last 5 years, from studies of early temperament, physiological reactivity, physical problems in reactive children and monkeys, and studies of some of the same gene-behavior associations that led to the vulnerability hypothesis.

For instance, one of the most robust associations supporting the vulnerability hypothesis is the link between depression and the so-called double short, or SS, version of the serotonin transporter gene, 5-HTTLPR, which affects the processing of serotonin, a key neurotransmitter important in mood. In 2003, psychiatrists Avshalom Caspi and Terrie Moffitt published a large, long-term study of New Zealanders that showed that if you're dealt the double short, or "bad," version of this gene (which can take three forms, or alleles: SS, or short-short; SL, or short-long; or LL, or long-long), you will be highly vulnerable to depression if (and only if) you have a difficult childhood or repeated serious traumas. The LL, or "good," version of the gene, meanwhile, seemed to grant its holders a profound

resilience: People with that version tended to let trouble roll off . People with the SL version had middling vulnerability. They found similar results with a "bad" and "good" version of the monoamine oxidase A, or MAOA, gene, which affects an array of neurotransmitters; people with the bad version tended to be more aggressive.

The Caspi and Moffitt study, more than any other, established the gene-environment interaction model of vulnerability. Since then, other studies have found similar associations regarding other genes. For instance, several studies have confirmed that people with certain versions of the MAOA gene are more prone to aggression and even sociopathy if raised in abusive homes. And people with "long-repeat" versions of the DRD4 gene, which influences sensitivity to dopamine (a neurotransmitter vital to learning, reward, risk, and emotional processing), were shown to be have greater propensity for ADHD, autism, novelty (or "thrill") seeking, and even schizophrenia if they were raised in or repeatedly exposed to troubled environments.

In each case, a "bad" version of a particular gene seemed to confer vulnerability (but never advantage), while a "good" version of that gene granted resilience, even a sort of inoculation. (The good genes lead to efficient processing of the neurotransmitters in question; the bad genes to less efficient processing.)

But in the last few years, other studies (as well as closer looks at the founding studies) have suggested these "bad" genes have upsides. Briefly:

> *DRD4 and disruptive behavior.* Several studies have found that kids with the inefficient version of the DRD4 gene are more prone to disruptive or aggressive behavior. Lately several new studies have found measured heightened function as well — that while "bad gene" kids from from low-functioning homes showed more disruptive behaviors, "bad gene" kids from good homes actually demonstrated fewer disruptive behaviors than did "good gene" kids from good homes. The orchids either wilted or thrived.
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> *5-HTTLPR and depression.* Many studies have replicated Caspi and Moffit's finding that people with the SS allele of this gene are particularly prone to depression if they had difficult childhoods or disengaged or harsh parents. But a recent study found that people carrying the SS allele and raised in highly supportive homes actually suffered *less* depression later than did people with the "protective" LL allele raised in similar homes.
>
> *MAOA and antisocial behavior.* Same pattern here: There's a well-established association between a certain version of the MAOA gene and aggressive and antisocial behavior in kids from tough homes. But in a couple new studies, kids with this allele raised in good homes showed stronger social skills and less inappropriate aggression than did kids with the "good" MAOA gene raised in similarly good environments. Same orchid effect.

But perhaps the most provocative and complete set of evidence comes from a long, detailed study of rhesus monkeys done by Stephen Suomi of the National Institute of Child Health and Development. When Suomi described his work this spring at a child development

conference in Denver, tying it for the first time directly to this orchid hypothesis, he stunned a packed room.

For over 25 years, Suomi has been studying behavior in large groups of rhesus monkeys, including a multi-tribe troop of about 100 that lives outdoors in a semi-naturalistic setting at his Maryland field station. Early in this work he identified two behavioral types that each reliably account for about 5-10% of every generation: ”depressed” or “neurotic” monkeys who are withdrawn, tentative, and anxious; and “social misfit” monkeys who are (at least in this setting) inappropriately aggressive. The neurotics mature later but generally do okay; the misfits are usually driven from the tribe before or as they reach puberty and die, childless, by early adulthood.

By the late 1990s, when genetic testing became available, the serotonin transporter gene, 5-HTTLPR, had become suspect in depression and other behaviors, Suomi assayed his monkeys for this gene and found that the neurotics and most of the misfits had SS (or bad) versions. But he also found a sizable minority of “normal” monkeys with SS alleles. Why weren’t these SS monkeys neurotic or hyperaggressive? Turns out these normal-acting bad-gene monkeys were raised by good mothers, while the neurotics and misfits had been raised by neurotic, anxious, or aggressive mothers. Suomi was seeing this at about the same time Caspi and Moffitt were running their study — and he actually published his (in 2002) just before Caspi and Moffit did theirs. Together these studies helped create the picture of gene-environment vulnerability.

Since then, however, he has seen increasing evidence that these “bad-gene, good-environment” monkeys fare better overall than do their “good-gene, good-environment” peers. They excel in all the behavioral measures that produce poor scores in bad-gene/bad-parenting monkeys. For example, in a one-hour “cocktail hour” test — free access to alcohol — at which bad-gene/bad-home monkeys reliably get staggering drunk, these bad-gene/good-home monkeys — the orchid/greenhouse monkeys — drink less alcohol than even their good-gene/good-home peers do. And they do better in a global sense as well, finding better mates, raising healthier and more offspring, and (a huge advantage) occupying higher places in their tribes’ social structures.

These “bad-gene, good environment” monkeys, in short, are some of the most fit and successful monkeys in the colony.

A two-pronged evolutionary advantage

Just how do these orchid genes grant an adaptive edge?

The most obvious way is by producing the sort of heightened function Suomi and others have found among animals or people with the orchid alleles (the alleles formerly known as “bad”) from good homes. The greater sensitivity to context makes these individuals rise to greater heights in good conditions.

But what about the downside? Might the “bad” behaviors that come from orchid raised in

bad environments sometimes pay benefits? Indeed that's the thinking. For while the downside behavior of these less fortunate orchids is often dysfunctional, it can apparently be helpful often enough to help make the gene adaptive enough to hold a place in the gene pool. A few examples:

- [snipped, sorry]
- In humans, meanwhile, behaviors we generally see as dysfunctional can be adaptive in a number of scenarios, such as in warrior classes both in earlier times and in today's military, police, or special forces; in some other professions today (Wall Street comes to mind). Since most every society needs individuals and groups like these, there's always a place for such behavior to be adaptive (up to a point) — and a that place is bigger in areas or periods in which intergroup conflict is more common.
- Likewise there are always subenvironments -- conflict zones, rough parts of town, drug or crime cultures -- where aggressive behavior is adaptive. These environments can also reward certain expressions of "nervous" or withdrawn temperament. Just as lying low allows Suomi's nervous monkeys to survive, gain extra social insight, and have reproductive success (albeit at a lower social level than others), so judiciously avoiding confrontation can allow an unassertive person to survive and have a family even in tough environments.
- Thus inefficient or "bad" genes reliably hold a place in normal environments, fair environments, and even in many harsh environments where a behavior or temperament maladaptive in moderate environments might lend extra advantage. This has led one pair of theorists, developmental psychologists Bruce Ellis and Thomas Boyce, to propose a U-shaped relation between early adversity and reactivity and expression and prominence of these "orchid-gene" traits — with the more reactive individuals showing more volatility (and gaining more relative advantage) in both extremely tough environments (at the left end of the U-shaped curve) and highly amenable environments (at the right end).*

In a way, this is another way of saying that extreme conditions reward extreme behavior. A major challenge rewards either fight or flight but takes a heavy toll on those who stand still. Likewise, times of great opportunity especially reward those who react with particular energy and initiative -- while the steady will survive, but not particularly excel.

The key to weedyness?

To Stephen Suomi, these dynamics — and the particular way the genes have emerged in rhesus monkeys and humans — suggest a novel explanation for humanity's unprecedented success and spread across the globe.

Suomi has long known that rhesus monkeys and humans are the only two "weed" species" among primates — species, that is, they can live in almost any environment. Other primates — all the other monkeys, and apes such as chimps and gorillas, too — can thrive only in their specific environments. Move them and they'll perish.

For years, the main implication this had for Suomi was that he can study the monkeys in a naturalistic environment in Maryland rather than in their native Asian habitats. But as the genomes of the various nonhuman primate species were analyzed over the last few years, the weed-species status of humans and rhesus took on a more profound implication. For it turns out that rhesus and humans are also the only primate species that carry an SS version of 5-HTTLPR. And while we still haven't tested all other primates for all the other key polymorphisms (MAOA, DRD4, and so on), the testing we do have so far have found few other primates with inefficient versions of those other genes. So it appears that rhesus monkeys and humans alone have developed polymorphisms in multiple key behavioral genes. (It also appears that they did so largely on separate tracks, since most of the polymorphisms whose origins have been dated in humans apparently developed only in the last 100,000 years — much more recently than our ancestral split, some 20 million years ago, from the line that became rhesus monkeys.)

"Now, I don't want to make too much of this too soon," Suomi told me. "But you can't help but wonder if this extra flexibility [derived from these polymorphisms] has contributed in some vital way to the success of these species." It's possible that our particular array of orchid genes,l which happen to bring us some of our biggest troubles — depression, hyperaggression and social strife, anomie and alienation — may well underlie much of our astounding success.

- It's important to note that Suomi and others assumes these effects work on multigenic levels, so that the more of these key orchid alleles you have, the more reactive you'll be. They also assume that genes affect one another in rich ways, much as people do. This makes these genetic effects all the more probabilistic and various (rather than deterministic) — and helps account for the great variety of temperament and personality. These interplays can not only determine what we might call a person's hue — the color of their personality and temperament — but how that hue may be denser at some times of life than others.

- This model also assumes and recognizes that people (and rhesus monkeys) have become weedy and particularly successful because they layer this extra genetic flexibility atop their species' social and cooperative natures. Many primate species depend heavily on sophisticated social relations for their success. Rhesus monkeys and humans add to this social strength a polymorphic intragroup variability that give them a larger and more flexible array of temperaments and talents than other primates. These genetic advantages then, benefit not just individuals and their families but the larger social groups (monkey troops, human communities) those families are part of. As Olivia Judson noted in her "Selfless Gene" piece for you a couple years ago, this community-level dynamic goes against much dogma and doctrine about genetics and evolution. Yet to Suomi and other observers, these polymorphisms contribute in vital ways not only to individual and family success but to the peculiar success that these two polymorphic-rich species have enjoyed.

This orchid hypothesis, has some big implications:.

- For starters, it recasts certain genetic "risks" as genetic bets — investments that

can go bad at times in many environments but which can bring high returns in extreme environments.

- This in turn paints a very different conception of mental illness or genetically based social dysfunction — one that recognizes that the most vulnerable are also the most responsive to change, especially early in their lives.

- This raises immense but tricky implications for early childhood interventions; these I discussed in [clipped], who was enthralled with the implications of this hypothesis. Although it would be politically and culturally complicated (to say the least), one could — if one wanted to maximize return on social investment in early childhood interventions — use these orchid gene variations to identify kids who stand both to gain and to lose most (those with orchid genes but bad environments) in order to direct substantial resources at them. (Indeed, at least one experimental drug-abuse intervention program has already done so.) For while a dandelion kid in a bad home will probably be little affected by any but drastic changes in his environment, an orchid kid will presumably go from wilting to flourishing — and contribute far more to his own life and society alike — if you turn his crack in the pavement into a greenhouse.

- Finally, there are immense evolutionary implications. As Suomi and others have noted, the potential adaptive benefits of these leveraged bets are enormous, particularly for parents or species that always have both dandelions and orchids in their offspring: They are the evolutionary equivalent of investing in both bond money market funds and aggressive growth funds. For having both dandelion and orchid kids wildly raises a family's (and a species') chance of succeeding in any environment, especially over time. This diversified bet provides precisely what's needed to spread and dominate across a changing world: The dandelions let you establish yourself almost anywhere, while the orchids let you attain otherwise unreachable heights once you're established yourself and can manipulate the environment.

I think this is a big story. I'd tell it by drawing on the material described above; on research and commentary from other researchers in genetics, development, evolutionary anthropology, ethology, and psychiatry; on work by [clipped]; and —[clipped].

Depending on how much we wanted to explore the intervention implications, we could also look at some experimental interventions programs as well. Finally, I might find out my own genetic makeup in these key genes (I have my suspicions ...) and ponder those implications.

I can report this story this summer and early fall and deliver later in autumn. [Note: As it turned out, the magazine wanted the story asap, as a feature due to run soon had collapsed; they asked me if I could do the story in 7 weeks, and I did.] Being rather rich in ideas, data, study material, and implication, it seems to me a longish story. This is a chance to have the first deep description of a major new explanation of both human dysfunction and human success.

*Don had three questions about this dynamic:

1.) Has this dynamic shown up yet in any actual community-level gene analyses? The answer is a provisional Yes — provisional because no large studies have looked closely at the upside of the inefficient/bad genes, i.e., the right-hand quarter of the U-shaped curve. However, that curve can be inferred sketched in lightly in pencil, as it were, by the lower rate of *negative* outcomes in "bad gene/good home" people in large studies like Caspi and Moffit's. That and other studies have shown that people or animals with the orchid alleles and good early environments have fewer negative outcomes -- that is, lower rates of depression, aggression, distractibility, disruptive behavior, etc. This absence of bad effects suggests better overall health and functioning and supports the smaller studies (like Suomi's cocktail-hour study) that show direct evidence of better function.

2.) What dictates the mix of dandelion and orchid alleles in a population? The assumption is that since both extremely harsh and extremely nurturing environments especially reward the more reactive orchid genes, those genes would spread in such extreme environments and fall back to more moderate numbers in moderate environments.

3) Does Suomi have any data showing whether more dominant or elite groups have high percentages of individuals with orchid genes in them? He does not have that data yet, though he is working on getting it.