HEALTH AND STRESS

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STRESS, SCHIZOPHRENIA & ADDICTION - IN OUR GENES?

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Some individuals are aggressive and extraverted while others tend to be timid and keep their feelings concealed. These and other traits are determined by both inherited and environmental influences. Which one of these ultimately proves to be the most important in shaping how we perceive things or react to stressful situations can be difficult to predict and may also vary for each of us.

With respect to physical features, whether we will be tall or short, have a cleft chin, or dimples is primarily preordained. **The genes we inherit from both parents remain permanent throughout life but whether they are expressed depends on several factors.** Genes for black or curly hair and brown eyes are dominant while those for blond hair, straight hair and blue eyes are recessive. Thus, you will tend to have dark, curly hair and brown eyes unless both your parents passed on the genes for blue eyes, blond and straight hair. However, other influences may determine the final results.

Parents with black or brunette hair tend to have dark-haired children who might still have recessive genes that would be passed on to succeeding generations. People with auburn hair undoubtedly had ancestors with red hair somewhere in their lineage even if there is no record of this. The gene for red hair is on a different chromosome. If two are inherited, your hair will be more intensely red compared to only one, and if absent, there is no reddish hue. The final shade depends on other factors since the darker the hair color the more the redness will be masked. Blond-haired children with two red genes will likely wind up as flaming red heads.

To further complicate things, hair color is determined by the amount and type of melanin made by pigment producing cells. The more densely melanin granules are packed together the darker the hair. Eumelanin makes brown hair darker and pheomelanin gives yellow-blond hair a reddish color. While genes influence melanin production, the amount that is manufactured depends on how the body metabolizes a molecule called tyrosine. Copper is a crucial

ALSO INCLUDED IN THIS ISSUE

component in this process. When dietary intake of copper is adequate tyrosine is completely broken down and plenty of melanin is accessible to give hair a darker color. If there is a deficiency of copper new hair growth will be light regardless of your genes. When the cells that produce pigment fail to function as we age, any new hair that grows in will be gray or white.

Schizophrenia, Cats And Litter Boxes

Eye color also depends on melanin content and some people can have one brown and one blue eye. How hair or eye color is determined is complicated but not nearly as complex as trying to figure out how genes influence personality and behavior. Identical twin studies show that although they share the very same genes, their traits and behaviors are often far from identical, especially when they are reared in different homes. In one report on 68 pairs of identical twins, one of who was schizophrenic, there were 28 instances where the other twin remained completely normal. In addition, none of the abnormalities in brain function on imaging studies often seen in schizophrenia were seen in the healthy twin.

Up until a few decades ago, psychiatrists blamed schizophrenia on bad mothers and/or poor parenting. However, heredity must play some role since children of schizophrenics are ten times more likely to develop the disorder than others without a family history. **Identical twins have the same genes but this only occurs in 50% of fraternal twins. If a gene caused schizophrenia then one would suspect that identical twins should be affected twice as much as both fraternal twins, whereas the actual ratio is closer to five to one.**

What causes these differences seems to be whether or not a gene is "expressed" or "turned on" by physical, emotional, and/or environmental factors. In schizophrenia, some suspect that this could be due to an infection, emotional stress or some combination of both. There is increasing evidence that the disorder can be triggered by fetal exposure to certain infections during pregnancy. **Schizophrenia usually starts in the late teens or twenties and researchers report that the number of young people in whom the diagnosis was first established tended to peak all over the world about two decades following flu epidemics.**

In addition to flu, herpes, Borna viruses and parasites carried by cats have also been implicated. One study found that 51 percent of schizophrenics had cats at home when they were kids, compared to only 38 percent of a control group. It has been observed that **schizophrenics are more likely to have been born in late winter or early spring when cats stay inside and use their litter boxes more. In addition, schizophrenia was relatively rare in Europe until the late 19th century, when cats first became popular as pets**.

Not much attention was paid to any of this until a 1999 study of 53,000 frozen blood samples taken from pregnant women during the 1950's in connection with a study being conducted on poliomyelitis. A Harvard researcher tracked down their offspring and zeroed in on 100 who had developed schizophrenia around two decades later. He found that their mothers had antibodies to *Toxoplasma gondii* at a rate 4.5 times higher compared to mothers with normal children and antibodies to herpes simplex virus were 7.5 times higher. Toxoplasma is a parasite found in cat feces that is usually destroyed by the immune system before it causes the disease toxoplasmosis. **If exposed to cat feces, a pregnant woman without any signs or symptoms of infection can still transmit the parasite to her fetus.**

Researchers believe that the organism lies dormant in brain cells until it is activated by some stressor. Why this should tend to take two decades to occur and vary from a progressive down hill course to intermittent episodes is not clear. Could stress be the culprit?

Genes, Stress And The "One-Two" Punch

It is rare for schizophrenia to begin before 16 or after 45 years of age with the average age of onset being in the mid-twenties. Although men and women are affected equally it tends to strike females later in life. Signs and symptoms frequently start to surface when susceptible individuals are subjected to stress, which may explain

some of these observations. Early adulthood can be one of the most stressful periods of life as individuals are striving to gain independence, secure a good job and develop close relationships. This is the most common time for schizophrenia to start in men. Major life stresses for women are more often related to problems related to pregnancy, childbirth and child-rearing that usually occur when they are a little older.

Several surveys have found that significantly stressful events such as a death of a family member, loss of a job, or break-up of a close relationship tend to make schizophrenia worse. Even seemingly mild stressful situations such as a job interview or a date can have a devastating effect. Studies also show that schizophrenics are more affected by physical as well as emotional stress as assessed by heart rate changes and higher rates of cardiovascular disease. This increased susceptibility to stress is consistent with the concept that schizophrenia is characterized by difficulties in filtering out what is happening in the outside world because of an inability to interpret social cues combined with faulty interpretations of internal thoughts and feelings.

Schizophrenia is not a discrete disease but rather a group of related psychiatric disturbances containing varying combinations of the following traits and behaviors:

- "Positive" psychotic symptoms manifested by paranoia, delusions and hallucinations
- "Negative" symptoms such as an apparent lack of emotion or motivation that produce passivity and a "flat affect"
- Cognitive defects that interfere with short term memory and concentrating abilities

Schizophrenics can sit quietly making little or no eye contact or act agitated as they experience elaborate hallucinations and delusions, as depicted in "*A Beautiful Mind*".

Genes, cat parasites, viruses and stress all seem to be risk factors for schizophrenia but what is the specific role of each? Why does it tend to begin in the second or third decade? Sophisticated brain-imaging technology has demonstrated that schizophrenia is as much an organic brain disorder, as is multiple sclerosis, Parkinson's or Alzheimer's disease. Is there any way to put all of this together?

The leading theory about the origin of schizophrenia is that the disease results, in part, from abnormal early development in susceptible individuals. This is supported by studies showing the existence of structural brain abnormalities long before the appearance of any psychiatric symptoms as well as an increased incidence of certain minor physical anomalies such as a high arched palate, asymmetrical ears, curved fifth finger and webbed toes. However, many individuals with these abnormalities never develop schizophrenia.

This has led to the "two-hit" or "one-two punch" hypothesis of schizophrenia: **genetic vulnerability and/or problems in the womb set the stage, but a second "hit" during early adulthood is what causes schizophrenia to surface**. Everyone's DNA has "endogenous retroviruses" that are vestiges of infections our ancestors once had. They are normally harmless, but if activated, begin causing disturbances in the hippocampus, a portion of the brain responsible for short-term memory and retrieval. The damage doesn't show up until the brain stops growing, which is in late adolescence, when schizophrenia tends to start.

Scientists believe that toxoplasma lies latent in brain cells until sometime between age 15 and 30 when it activates retroviruses that cause schizophrenia to develop. Increased stress is a likely candidate to be the culprit because it lowers the immune system's ability to inactivate unwanted microorganisms. **One comprehensive study confirmed that 46% of schizophrenic patients had experienced some significant stressful life event in the three months prior to the onset of symptoms.** Stress-related hormones like cortisol also cause hippocampal damage and problems with memory and concentration and elevated cortisol levels are common in schizoid adolescents.

Chromosomes, Genes, DNA And Genomes

The physical characteristics of children usually resemble those of one or both parents and in some instances, they can be the "spitting image" of a grandparent or some other ancestor. Although parents who are very short tend to have short offspring it is not unusual for one to be surprisingly tall. Relatives are apt to quickly identify some forbear who was well over six feet, explaining that the trait must have "skipped" a generation to avoid any suggestion that the milkman might have been involved. The same is true for behavioral characteristics as people are told they inherited Uncle Charlie's sense of humor and quick wit or somebody else's genes for bad temper.

Every cell in the body contains twenty-three pairs of chromosomes, one from each parent. Chromosomes are studded with genes and are composed of DNA (deoxyribonucleic acid), a complex molecule that determines various aspects of how we develop physically, and possibly emotionally. Watson and Crick shared a 1962 Nobel Prize for demonstrating that the structure of DNA was a double helix or twisted ladder whose rungs were composed of varied combinations of four proteins. Everyone has heard about DNA by now because its ability to determine the identity of individuals is superior to fingerprint analysis. DNA testing has been especially effective in determining paternity or establishing guilt and innocence based on evidence collected at crime scenes.

It was first used in the late 1980's to convict a man of raping and impregnating his 13 year-old daughter. DNA analysis of tissue taken from both the father and the aborted fetus were so conclusive that the man confessed. The test was remarkable because although the fetus contained both the man's and girl's DNA, scientists were still able to find specific sequences that proved the father's guilt. DNA testing has been increasingly used in courtrooms over the past decade, most notably as evidence in the O.J. Simpson trial. DNA analysis cleared Sam Sheppard, the physician who was convicted for brutally killing his wife but always insisted that a "bushy-haired" man did it. Such an individual was later identified.

DNA tests showed that some blood at the murder scene was not from Sheppard or his wife, proving that someone else was there, which inspired the TV series and movie, *The Fugitive*. DNA tests have freed so many thousands of suspected and convicted prisoners, including many on death row, that doubts are being raised about the reliability of the criminal justice system and current criteria for capital punishment. **The United States is the only Western democracy that carries out executions. European Union membership requires a country to abolish the death penalty.**

Genome is a term for all the inherited instructions required for the formation and function of an organism that will be passed on to succeeding generations. Genomes contain genes that are packaged in chromosomes composed of DNA. These relationships can be visualized as a set of Chinese boxes nested inside another. The largest box is the genome that holds a smaller box of chromosomes, inside of which is a box representing genes that contain the smallest box, the DNA. Every species on earth has its own distinct genome. There are genomes for different breeds of dogs, cows, flies, corn, wheat, bacteria, viruses and all living things, but the number of chromosomes they contain varies considerably. In simple organisms like bacteria the entire genome is contained in a single chromosome.

In general, similar species have similar numbers but there is no correlation based on the complexity of evolution. A mosquito has 6 chromosomes, a pea 14, a sunflower 34, a cat 38 and humans have 46; but chimpanzees have 48, dogs have 78 and goldfish have 94! The number of genes in a chromosome also varies widely and can range from 231 to 2,968 in humans. Although genomes belong to species, the genome and DNA sequencing pattern found in each of the trillions of cells in the human body is unique for every individual. **Unless you are an identical twin or are cloned, your genome is different from that of every other person who has ever lived or will live.** However, you will still show certain distinctions. Even identical twins have different fingerprints and numerous environmental factors influence how we finally develop.

Genetic Profiling - A Two-Edged Sword?

The Human Genome Project's roadmap of the human genome DNA sequencing pattern has identified about 30,000 genes, which is much less than the 100,000 originally predicted. It was hoped that this new data would allow doctors to detect diseases at earlier stages, improve diagnostic accuracy and make therapy safer and more focused by tailoring drugs to fit an individual's specific DNA sequence. Its publication early last year was preceded by a decade of hype about the discovery of genes for various malignancies, metabolic, musculoskeletal, neurologic and other diseases. In addition, there were claims that genes were responsible for or associated with traits and attributes as diverse as obesity, risk-taking, IQ, neurotic and psychotic disorders, addiction to alcohol, cigarettes and drugs, aggression and even views on the death penalty.

The significance of such relationships has stirred considerable controversy and revived the age-old debate over the relative significance of heritable and environmental factors in different disorders. To date, this has generated many more questions than answers and has also raised new concerns. Scientists have been able to identify DNA variations that are associated with certain malignancies, asthma, diabetes, hypertension, Alzheimer's and the way people react to certain drugs. However, the ability to uncover health risks could threaten obtaining employment or health and life insurance if our personal genetic profiles were made available to others.

One 46 year-old worker had always received excellent work reviews until she was diagnosed with a genetic lung disease that had killed her brother. It required treatment with an expensive drug and when her self-insured employer started receiving medical bills of almost $4,000/month, she was told that her services were no longer needed. Thirty states and the federal government have laws that prohibit denying employment or insurance based on genetic information but many feel that privacy should not depend on your zip code. As the NIH director of genome research noted, **"We don't get to pick our genes, so our genes shouldn't be used against us."**

Frankenstein From A Test Tube?

In addition to allowing more accurate identification of individuals, the ability to determine the exact nature of DNA sequencing has important medical implications. Two decades ago, David Baltimore and colleagues shared a Nobel Prize for determining the genetic sequence of the poliovirus. He also made a physical copy of its genetic nature and found that this clone could cause the infection when injected into experimental animals. **This was the first proof that DNA alone could be used to make a virus.** The DNA used came from living cells and scientists wondered if it would be possible to do the same thing by simply putting the correct chemicals into the proper sequence without using living cells.

A few months ago, researchers reported in *Science* that they had succeeded in synthetically replicating the poliovirus from scratch without the aid of any living cells. In addition, they showed that this artificial preparation could infect cells and cause paralysis in mice. This has important implications since it suggests that as long as you know the roadmap of DNA sequencing, it should be possible to reconstruct smallpox, herpes and other viruses. This would obviate the need to stockpile stores of smallpox virus to make vaccines in the event of biowarfare. It might also be possible to vary the genetic makeup of a virus to make safer and superior vaccines. The downside is that terrorists might use this technology to wreak widespread havoc.

That's not likely to happen soon since the polio virus genome is comparatively small, with a genetic code consisting of 7,741 molecular letters. Smallpox has almost 200,000 letters in a complex geometric code pattern that would be difficult to duplicate in a three-dimensional structure. Nevertheless, many scientists remain concerned and some called the publication of the paper in *Science* irresponsible. The American Association for the Advancement of Science, which publishes the journal, defended the article as an important scientific advance but admitted that they were now considering a formal policy on how to deal with potentially dangerous research reports.

The Fallacy Of Is It Nature Or Nurture?

Progress in characterizing the human genome offered the promise of learning more about the role of heredity and genes in different diseases and behaviors. Prenatal screening has been useful in identifying unaffected individuals who carry genes for certain disorders that might influence decisions about pregnancy. Testing newborns or asymptomatic individuals at high risk for Huntington's, Alzheimer's and other disease could also lead to discovering effective ways to prevent or delay their onset. Nevertheless, the more we understand how genes function the more the pendulum seems to swing towards environmental factors as being more important in determining health outcomes.

Genes simply contain the instructions for creating certain specific proteins. It is these proteins that actually determine such things as carotene in your hair, collagen in your skin or hemoglobin in your red blood cells. One gene can make multiple proteins, whose activities are modified by numerous environmental influences, as previously illustrated by the example of hair color. We may only have 30,000 genes, but they probably produce 100,000 distinct proteins that might result in a million modifications. **Knowing what genes you have is not the final answer.**

As one leading authority explained, a Boeing 777 has approximately 100,000 parts ranging from screws and wires to rudders and wings. You could have a list of all of these but that wouldn't tell you how to put them together correctly. Certain parts are more essential than others and some of them probably don't matter too much. If specific screws are missing or not in the right place it may merely mean that your arm rest or dinner tray will be loose or crooked. However, if they happen to be the screws on a propeller, it could be disastrous. A parts list provides important information about the composition of the plane but that's not enough to allow you to understand why it flies. The Human Genome Project is essentially little more than a parts list of our chromosomes and the genes they contain. It does not explain how they function or interact.

In the seesaw struggle between our genes (nature) and environmental influences (nurture), nurture is increasingly gaining the upper hand. We know that changes in specific genes cause certain diseases like cystic fibrosis because they are present in all such patients. However, if you study the rest of the population, many people with these identical genetic changes don't develop cystic fibrosis. Some get chronic lung disease, pancreatitis, male sterility, asthma or sinusitis and others may be perfectly healthy. These genes always produce the same proteins, but how these are modified by different environmental factors can vary tremendously.

For example, colon malignancies are often associated with a defective "colon cancer" gene. Patients carry this mutated gene in all of their cells so why is it that cancer occurs only in the colon? Researchers believe that toxins secreted by bacteria in the colon are what trigger malignant activity. Other studies have shown that heavy smokers have twice the incidence of cancer of the colon and rectum compared to controls with no exposure to tobacco. However, the colon has two regions. The distal or left side consists of the descending and sigmoid portion and the proximal or right side includes the caecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure. A recent study found that cigarette smoking was associated with an increase in cancer of the proximal colon and cigar smokers had higher rates of rectal cancer. **However, cigarette smoking actually protected against malignancies of the distal colon!** There was no obvious explanation for this although the researchers noted that smokers tend to eat more meat and less fruit and vegetables. These dietary habits are associated with less risk of distal cancer colon.

Despite a decade of headlines touting the discovery of a "breast cancer" and "colon cancer" gene, a Scandinavian study of 45,000 pairs of twins concluded that **cancer is caused more by environmental than inherited factors**. Almost everyone now agrees that whether we develop a disease or a specific trait is no longer a question of "Is It Nature or Nurture?" but depends on complex interactions between both.

Genes, Emotions And Behavioral Traits

The first scientist to systematically study whether genes could significantly influence behavior was Francis Galton, the Victorian psychologist and mathematician who invented fingerprint identification. A pioneer in the field of the significance of statistical correlation, he was convinced of the crucial role of heredity and coined the term "eugenics", meaning "well born". Galton studied groups of families to learn whether intelligence, violence, alcoholism and other aspects of social well being might be inherited in the belief that eugenics could improve the quality of the human species. His American disciple, Charles Davenport, continued the search for familial patterns in alcoholism, criminality, insanity and other traits believed to be passed on from prior generations. He and his colleagues also attributed certain characteristics to particular races and concluded that Italians were drawn to crimes of personal violence, Greeks were slovenly, Swedes tended to be tidy. Ethnic jokes persist about Irish and Polish "stupidity".

Eugenicists hoped to eliminate social problems in the U.S. through immigration restrictions and involuntary sterilization and abortion legislation. By 1935, thirty states had passed sterilization laws to prevent reproduction by genetically "inferior" people. Hitler expanded on this to justify massive sterilization and extermination programs and although Nazi atrocities discredited the eugenics movement, involuntary sterilization persisted in the U.S. until 1973. As of 1985, some twenty states still had laws permitting the sterilization of people with mental disabilities.

Traits such as elaborate mating rituals are undoubtedly species specific in certain birds and animals. A chickadee will carry one sunflower seed at a time from a feeder to a nearby branch, secure it between its feet, peck it open, eat the contents, and keep repeating this. Finches stay at the feeder for long periods of time opening large numbers of seeds with their thick beaks. Labradors have instinctive retrieval behaviors, Collies have herding tendencies, Dobermans are protective and all these traits persist regardless of the environment.

Traits in humans can be more difficult to define. **Is intelligence being able to solve certain problems and score high on IQ tests, or common sense that allows you to excel in dealing with daily challenges?** In one report, the learning ability of mice was significantly improved by inserting a gene that makes a protein in brain cells associated with memory storage and retrieval. The media named it the "IQ gene", as if memory was the most important criterion for defining intelligence. However, some idiot savants can perform incredible memory feats and there is no universal agreement on how best to define intelligence.

Studies on mice are a convenient way to investigate the genetic roots of behavior since the components of the mouse genome are surprisingly similar to ours but are arranged in a different order. Scientists have learned how to breed strains of "knockout mice" in whom certain genes are inactivated to study their effects. One such strain without a particular receptor for serotonin showed belligerent behavior and seemed unusually attracted to and tolerant of alcohol. Another strain missing a gene to produce nitric oxide acted extremely aggressive and violent when challenged.

Other researchers hunt for strains of mice that crave alcohol or behave in a certain way and then look for the responsible gene. Once this has been identified they try to determine if its human counterpart has a similar effect - but it's not that simple. In one study of mice that kept returning to a morphine-laced drinking bottle, the explanation turned out to be not that they had an "addiction gene" but rather hated the taste of the quinine in the alternative choice. Does a mouse that strikes at another rodent on top of its cage have a gene that makes it aggressive, or could it simply be more anxious, claustrophobic and sensitive to a sudden shadow?

Researchers recently reported finding an "anxiety gene" that makes people significantly more reactive to stress because of effects on serotonin. While sophisticated imaging studies confirmed greater activity in portions of the brain activated during stress, this has little practical significance. **Our responses to stress depend mostly on environmental influences.**

How Stress Influences Health And Behavior By Turning Genes On And Off

In addition, **even if you have a trait-related gene it will have no effect if it is "turned off"**. It has been well established that stress and stress-related hormones like cortisol lower immune system defenses to microbial invaders. Research in medical students subjected to the strains of final exams confirmed that those who scored high on stress measurements had a correspondingly high incidence of upper respiratory infections. Further investigation revealed that genes in certain white cells that normally produce proteins to recognize foreign intruders had become inactivated and could not detect or combat these bacteria and viruses. Studies suggest that stress-induced suppression of gene expression may explain chronic disorders such as post-traumatic stress syndrome. Early environmental influences not only affect gene expression but also how the organism responds to stress later on. **How much a mother rat handles and licks her offspring determines whether genes for stress hormone receptors in the brain will be expressed. Rats raised by attentive moms were less fearful and more curious compared to those who received less maternal grooming** and grew up to be timid and withdrawn when exposed to challenges.

Trying to comprehend how heredity influences human behavior requires analyzing groups of people to determine whether the presence or absence of specific genes correlates with certain traits. This provides statistics about what might possibly be due to genetic factors but does not predict what is likely to result in anyone not in that exact environment. Identical twins are often studied because of startling similarities in those that are raised apart. However, there may be explanations other than genetics since individuals with the same physical features tend to be treated alike and thus may share developmental experiences. Identical twins may both be tall and society tends to treat taller people with more respect, attention and reinforcement, all of which are likely to increase self esteem. Such twins would probably both score high for self-confidence and extraversion on personality tests, but not because they both inherited any "self esteem" gene.

While terms like "genetic", "inherited" and "familial" are often used interchangeably, they are not synonymous. The first two involve the physical transfer of genes from a preceding generation while "familial" simply means that a trait occurs at a higher rate within a family. This could be due to inherited or environmental influences but is usually some combination of both, as illustrated by the effect of stressful life change events in triggering schizophrenia**. Even feelings and thoughts can "turn on" genes.** One individual confined for several weeks on a remote island in comparative isolation reported that the day before he was due to leave, his beard began to sprout in a remarkable fashion. The most likely explanation is that the stimulus for this sudden luxurious growth was related **to the anticipation of sexual activity** that would soon follow and that his libidinous thoughts and feelings had unleashed a flood of testosterone. What turns genes on and off may be more important than their presence. Stress can play a crucial role in this, so stay tuned!

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