THE BLUE PEOPLE OF TROUBLESOME CREEK

The story of an Appalachian malady, an inquisitive doctor, and a paradoxical cure.

by Cathy Trost

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Six generations after a French orphan named Martin Fugate settled on the banks of eastern Kentucky's Troublesome Creek with his redheaded American bride, his great-great-great great grandson was born in a modern hospital not far from where the creek still runs.

The boy inherited his father's lankiness and his mother's slightly nasal way of speaking.

What he got from Martin Fugate was dark blue skin. "It was almost purple," his father recalls.

Doctors were so astonished by the color of Benjy Stacy's skin that they raced him by ambulance from the maternity ward in the hospital near Hazard to a medical clinic in Lexington. Two days of tests produced no explanation for skin the color of a bruised plum.

A transfusion was being prepared when Benjy's grandmother spoke up. "Have you ever heard of the blue Fugates of Troublesome Creek?" she asked the doctors.

"My grandmother Luna on my dad's side was a blue Fugate. It was real bad in her," Alva Stacy, the boy's father, explained. "The doctors finally came to the conclusion that Benjy's color was due to blood inherited from generations back."

Benjy lost his blue tint within a few weeks, and now he is about as normal looking a seven-year-old boy as you could hope to find. His lips and fingernails still turn a shade of purple-blue when he gets cold or angry a quirk that so intrigued medical students after Benjy's birth that they would crowd around the baby and try to make him cry. "Benjy was a pretty big item in the hospital," his mother says with a grin.

Dark blue lips and fingernails are the only traces of Martin Fugate's legacy left in the boy; that, and the recessive gene that has shaded many of the Fugates and their kin blue for the past 162 years.

They're known simply as the "blue people" in the hills and hollows around Troublesome and Ball Creeks. Most lived to their 80s and 90s without serious illness associated with the skin discoloration. For some, though, there was a pain not seen in lab tests. That was the pain of being blue in a world that is mostly shades of white to black.

There was always speculation in the hollows about what made the blue people blue: heart disease, a lung disorder, the possibility proposed by one old-timer that "their blood is just a little closer to their skin." But no one knew for sure, and doctors rarely paid visits to the remote creekside settlements where most of the "blue Fugates" lived until well into the 1950s. By the time a young hematologist from the University of Kentucky came down to Troublesome Creek in the 1960s to cure the blue people, Martin Fugate's descendants had multiplied their recessive genes all over the Cumberland Plateau.

Madison Cawein began hearing rumors about the blue people when he went to work at the University of Kentucky's Lexington medical clinic in 1960. "I'm a hematologist, so something like that perks up my ears," Cawein says, sipping on whiskey sours and letting his mind slip back to the summer he spent "tromping around the hills looking for blue people."

Cawein is no stranger to eccentricities of the body. He helped isolate an antidote for cholera, and he did some of the early work on L-dopa, the drug for Parkinson's disease. But his first love, which he developed as an Army medical technician in World War II, was hematology. "Blood cells always looked so beautiful to me," he says.

Cawein would drive back and forth between Lexington and Hazard an eight-hour ordeal before the tollway was built and scour the hills looking for the blue people he'd heard rumors about. The American Heart Association had a clinic in Hazard, and it was there that Cawein met "a great big nurse" who offered to help.

Her name was Ruth Pendergrass, and she had been trying to stir up medical interest in the blue people ever since a dark blue woman walked into the county health department one bitterly cold afternoon and asked for a blood test.

"She had been out in the cold and she was just blue!" recalls Pendergrass, who is now 69 and retired from nursing. "Her face and her fingernails were almost indigo blue. It like to scared me to death! She looked like she was having a heart attack. I just knew that patient was going to die right there in the health department, but she wasn't a'tall alarmed. She told me that her family was the blue Combses who lived up on Ball Creek. She was a sister to one of the Fugate women." About this same time, another of the blue Combses, named Luke, had taken his sick wife up to the clinic at Lexington. One look at Luke was enough to "get those doctors down here in a hurry," says Pendergrass, who joined Cawein to look for more blue people.

Trudging up and down the hollows, fending off "the two mean dogs that everyone had in their front yard," the doctor and the nurse would spot someone at the top of a hill who looked blue and take off in wild pursuit. By the time they'd get to the top, the person would be gone. Finally, one day when the frustrated doctor was idling inside the Hazard clinic, Patrick and Rachel Ritchie walked in.

"They were bluer'n hell," Cawein says. "Well, as you can imagine, I really examined them. After concluding that there was no evidence of heart disease, I said 'Aha!' I started asking them questions: 'Do you have any relatives who are blue?' then I sat down and we began to chart the family."

Cawein remembers the pain that showed on the Ritchie brother's and sister's faces. "They were really embarrassed about being blue," he said. "Patrick was all hunched down in the hall. Rachel was leaning against the wall. They wouldn't come into the waiting room. You could tell how much it bothered them to be blue."

After ruling out heart and lung diseases, the doctor suspected methemoglobinemia, a rare hereditary blood disorder that results from excess levels of methemoglobin in the blood. Methemoglobin which is blue, is a nonfunctional form of the red hemoglobin that carries oxygen. It is the color of oxygen-depleted blood seen in the blue veins just below the skin.

If the blue people did have methemoglobinemia, the next step was to find out the cause. It can be brought on by several things: abnormal hemoglobin formation, an enzyme deficiency, and taking too much of certain drugs, including vitamin K, which is essential for blood clotting and is abundant in pork liver and vegetable oil.

Cawein drew "lots of blood" from the Ritchies and hurried back to his lab. He tested first for abnormal hemoglobin, but the results were negative.

Stumped, the doctor turned to the medical literature for a clue. He found references to methemoglobinemia dating to the turn of the century, but it wasn't until he came across E. M. Scott's 1960 report in the Journal of Clinical Investigation (vol. 39, 1960) that the answer began to emerge.

Scott was a Public Health Service doctor at the Arctic Health Research Center in Anchorage who had discovered hereditary methemoglobinemia among Alaskan Eskimos and Indians. It was caused, Scott speculated, by an absence of the enzyme diaphorase from their red blood cells. In normal people hemoglobin is converted to methemoglobin at a very slow rate. If this conversion continued, all the body's hemoglobin would eventually be rendered useless. Normally diaphorase converts methemoglobin back to hemoglobin. Scott also concluded that the condition was inherited as a simple recessive trait. In other words, to get the disorder, a person would have to inherit two genes for it, one from each parent. Somebody with only one gene would not have the condition but could pass the gene to a child.

Scott's Alaskans seemed to match Cawein's blue people. If the condition were inherited as a recessive trait, it would appear most often in an inbred line.

Cawein needed fresh blood to do an enzyme assay. He had to drive eight hours back to Hazard to search out the Ritchies, who lived in a tapped-out mining town called Hardburly. They took the doctor to see their uncle, who was blue, too. While in the hills, Cawein drove over to see Zach (Big Man) Fugate, the 76-year-old patriarch of the clan on Troublesome Creek. His car gave out on the dirt road to Zach's house, and the doctor had to borrow a Jeep from a filling station.

Zach took the doctor even farther up Copperhead Hollow to see his Aunt Bessie Fugate, who was blue. Bessie had an iron pot of clothes boiling in her front yard, but she graciously allowed the doctor to draw some of her blood.

"So I brought back the new blood and set up my enzyme assay," Cawein continued. "And by God, they didn't have the enzyme diaphorase. I looked at other enzymes and nothing was wrong with them. So I knew we had the defect defined.''

Just like the Alaskans, their blood had accumulated so much of the blue molecule that it over- whelmed the red of normal hcmoglobin that shows through as pink in the skin of most Caucasians.

Once he had the enzyme deficiency isolated, methylene blue sprang to Cawein's mind as the "perfectly obvious" antidote. Some of the blue people thought the doctor was slightly addled for suggesting that a blue dye could turn them pink. But Cawein knew from earlier studies that the body has an alternative method of converting methemoglobin back to normal. Activating it requires adding to the blood a substance that acts as an "electron donor." Many substances do this, but Cawein chose methylene blue because it had been used successfully and safely in other cases and because it acts quickly.

Cawein packed his black bag and rounded up Nurse Pendergrass for the big event. They went over to Patrick and Rachel Ritchie's house and injected each of them with 100 milligrams of methylene blue.

''Within a few minutes. the blue color was gone from their skin," the doctor said. "For the first time in their lives, they were pink. They were delighted."

"They changed colors!" remembered Pendergrass. "It was really something exciting to see."

The doctor gave each blue family a supply of methylene blue tablets to take as a daily pill. The drug's effects are temporary, as methylene blue is normally excreted in the urine. One day, one of the older mountain men cornered the doctor. "I can see that old blue running out of my skin," he confided.

Before Cawein ended his study of the blue people, he returned to the mountains to patch together the long and twisted journey of Martin Fugate's recessive gene. From a history of Perry County

and some Fugate family Bibles listing ancestors, Cawein has constructed a fairly complete story.[see inferred Pedigree on right; more accurate pedigree below]

Martin Fugate was a French orphan who emigrated to Kentucky in 1820 to claim a land grant on the wilderness banks of Troublesome Creek. No mention of his skin color is made in the early histories of the area, but family lore has it that Martin himself was blue.

The odds against it were incalculable, but Martin Fugate managed to find and marry a woman who carried the same recessive gene. Elizabeth Smith, apparently, was as pale-skinned as the mountain laurel that blooms every spring around the creek hollows.

Martin and Elizabeth set up housekeeping on the banks of Troublesome and began a family. Of their seven children, four were reported to be blue.

The clan kept multiplying. Fugates married other Fugates. Sometimes they married first cousins. And they married the people who lived closest to them, the Combses, Smiths, Ritchies, and Stacys. All lived in isolation from the world, bunched in log cabins up and down the hollows, and so it was only natural that a boy married the girl next door, even if she had the same last name.

"When they settled this country back then, there was no roads. It was hard to get out, so they intermarried," says Dennis Stacy, a 51-year-old coal miner and amateur genealogist who has filled a loose-leaf notebook with the laboriously traced blood lines of several local families.

Stacy counts Fugate blood in his own veins. "If you'll notice," he observes, tracing lines on his family's chart, which lists his mother's and his father's great grandfather as Henley Fugate, "I'm kin to myself."

The railroad didn't come through eastern Kentucky until the coal mines were developed around 1912, and it took another 30 or 40 years to lay down roads along the local creeks.

Martin and Elizabeth Fugate's blue children multiplied in this natural isolation tank. The marriage of one of their blue boys, Zachariah, to his mother's sister triggered the line of succession that would result in the birth, more than 100 years later, of Benjy Stacy.

When Benjy was born with purple skin, his relatives told the perplexed doctors about his great grandmother Luna Fugate. One relative describes her as "blue all over," and another calls Luna "the bluest woman I ever saw."

Luna's father, Levy Fugate, was one of Zachariah Fugate's sons. Levy married a Ritchie girl and bought 200 acres of rolling land along Ball Creek. The couple had eight children, including Luna.

A fellow by the name of John E. Stacy spotted Luna at Sunday services of the Old Regular Baptist Church back before the century turned. Stacy courted her, married her, and moved over from Troublesome Creek to make a living in timber on her daddy's land.

Luna has been dead nearly 20 years now, but her widower survives. John Stacy still lives on Lick Branch of Ball Creek. His two room log cabin sits in the middle of Laurel Fork Hollow. Luna is buried at the top of the hollow. Stacy's son has built a modern house next door, but the old logger won't hear of leaving the cabin he built with timber he personally cut and hewed for Luna and their 13 children.

Stacy recalls that his father-inlaw, Levy Fugate, was "part of the family that showed blue. All them old fellers way back then was blue. One of 'em I remember seeing him when I was just a boy Blue Anze, they called him. Most of them old people went by that name the blue Fugates. It run in that generation who lived up and down Ball [Creek]."

"They looked like anybody else, 'cept they had the blue color," Stacy says, sitting in a chair in his plaid flannel shirt and suspenders, next to a cardboard box where a small black piglet, kept as a pet, is squealing for his bottle. "I couldn't tell you what caused it."

The only thing Stacy can't or won't remember is that his wife Luna was blue. When asked ahout it, he shakes his head and stares steadfastly ahead. It would be hard to doubt this gracious man except that you can't find another person who knew Luna who doesn't remember her as being blue.

"The bluest Fugates I ever saw was Luna and her kin," says Carrie Lee Kilburn, a nurse who works at the rural medical center called Homeplace Clinic. "Luna was bluish all over. Her lips were as dark as a bruise. She was as blue a woman as I ever saw."

Luna Stacy possessed the good health common to the blue people, bearing at least 13 children before she died at 84. The clinic doctors only saw her a few times in her life and never for anything serious.

As coal mining and the railroads brought progress to Kentucky, the blue Fugates started moving out of their communities and marrying other people. The strain of inherited blue began to disappear as the recessive gene spread to families where it was unlikely to be paired with a similar gene.

Benjy Stacy is one of the last of the blue Fugates. With Fugate blood on both his mother's and his father's side, the boy could have received genes for the enzyme deficiency from either direction. Because the boy was intensely blue at birth but then recovered his normal skin tones, Benjy is assumed to have inherlted only one gene for the condition. Such people tend to be very blue only at birth, probably because newborns normally have smaller amounts of diaphorase. The enzyme eventually builds to normal levels in most children and to almost normal levels in those like Benjy, who carry one gene.

Hilda Stacy (nee Godsey) is fiercely protective of her son. She gets upset at all the talk of inbreeding among the Fugates. One of the supermarket tabloids once sent a reporter to find out about the blue people, and she was distressed with his preoccupation with intermarriages.

She and her husband Alva have a strong sense of family. They sing in the Stacy Family Gospel Band and have provided their children with a beautiful home and a menagerie of pets, including horses.

"Everyone around here knows about the blue Fugates," says Hilda Stacy who, at 26, looks more like a sister than a mother to her children. "It's common. It's nothing.''

Cawein and his colleagues published their research on hereditary diaphorase deficiency in the Archives of Internal Medicine (April, 1964) in 1964. He hasn't studied the condition for years. Even so, Cawein still gets calls for advice. One came from a blue Flugate who'd joined the Army and been sent to Panama, where his son was born bright blue. Cawein advised giving the child methylene blue and not worrying about it. Note: In this instance the reason for cyanosis was not methemoglobinemia but Rh incompatibility. This information supplied by John Graves whose uncle was the father of the child.

The doctor was recently approached by the producers of the television show "That's Incredible." They wanted to parade the blue people across the screen in their weekly display of human oddities. Cawein would have no part of it, and he related with glee the news that a film crew sent to Kentucky from Hollywood fled the "two mean dogs in every front yard" without any film. Cawein cheers their bad luck not out of malice but out of a deep respect for the blue people of Troublesome Creek.

"They were poor people," concurs Nurse Pendergrass, "but they were good."

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Pedigree of Methemoglobinemia

Pedigree information graciously provided by Mary D. Fugate, publisher of The

Fugate Family Newsletter.

Curing the Kentucky Blues

Dr. Madison Cawein was a hematologist at the University of Kentucky Medical Center when he heard stories about the blue people of Troublesome Creek. He scoured the area around Hazard, Kentucky, trying to find the blue people but to no avail until Patrick and Rachel Ritchie, a brother and sister and both blue, walked into the Hazard clinic on a day when Cawein was there. He checked to make sure the siblings had no heart problems and then he began asking about their families and other blue people. He had found the descendants of Martin Fugate.

Dr. Cawein drew blood and eventually demonstrated that the problem was a deficiency of NADH diaphorase. He went out into the hills and found other blue people including Zach Fugate and his Aunt Bessie Fugate all living near a nearly dead mining town known as Hardburly.

The doctor had noticed that the blue people were not particularly happy about being blue. So, he hit upon a particularly brilliant scheme to help them. He knew that a second enzyme could do the trick if a good reducing agent was present. So, he injected Patrick and Rachel with methylene blue and within a few minutes, they both turned pink! They were delighted. The change was only transient but he left them some methylene blue pills to take on a daily basis and it worked. In fact, the mountain people could see the blue leaving their bodies since some of the methylene blue was excreted in their urine. One of the older mountain men confided to Dr. Cawein, "I can see that old blue running out of my skin."

The doctor never did reveal the location of the blue people and what with a daily dose of methylene blue, it may be that no one will ever find them again.

Curing the Blues in Ireland

adapted from Am. J. Haem 42: 3-6, 1993

Prior to WWII, Dr. Deeny practiced medicine in Bainbridge, Ireland, a town of about 5,000. He was sure that he could treat the cyanosis associated with heart failure by dosing the patients with a reducing agent such as ascorbic acid.

One morning in his office, he saw outside a deeply cyanosed man walk by! Unable to get outside to stop the man, he went to the local police station and asked if they knew of a blue man in the locality. Dr. Deeny was told there were two, blue men! "Fred and Russell, brothers you know." Deeny had not know about them because the brothers were Protestant while Deeny was Catholic.

He called on the brothers and asked if they would like to be pink. They agreed to his experiment. So, Dr. Deeny did a controlled experiment and gave one brother a daily dose of ascorbic acid (vitamin C) while the other received a placebo. The treated brother turned pink while the control remained blue.

The Chemistry and Genetics

The Blue Families carry an ineffective allele of the gene for NADH Diaphorase. NADH Diaphorase is an enzyme that repairs hemoglobin when it has been damaged by oxidation, leaving the iron atom in the +3 state. However, if the enzyme is inactive due to DNA sequence variation, then damaged hemoglobin cannot be repaired, and accumulates--producing blue skin color.

Dr. Cawein, of The Blue People of Troublesome Creek and Curing the Kentucky Blues, used methylene blue to repair the damaged hemoglobin. That is, methylene blue, in its reduced form, is a colorless, water-solulble molecule. When it has been oxidized, it becomes blue. The blue tint that this gives to urine accounts for the last quote in Kathy Trost's article, that "I can see that old blue running out of my skin." The use of vitamin C by Dr. Deeny in Ireland achieves the same result of repairing damaged hemoglobin. However, vitamin C is colorless, so there is no excretion of blue pigment.

The blue trait is a good example of something that does not fit the traditional view of alleles as being dominant or recessive. A person carrying one copy of the "blue allele" of ND has more total ND enzyme than does a person carrying two copies of the"blue allele," and thus the blue characteristics are much less pronounced; the "blue allele" is recessive. But the blue characteristics are not altogether absent (note the blueness at birth, and the blueness of lips and fingernails), so this allele does not fit the typical definition of "recessive." In fact, most genetic variation reflects alleles that are neither strictly dominant nor strictly recessive; gradations, such as that we see here, are the norm.









DETAILED CASE ANALYSIS

for

“Those Old Kentucky Blues: An Interrupted Case Study”

by

Celeste A. Leander, Departments of Botany and Zoology, University of British Columbia

Robert J. Huskey, Department of Biology, University of Virginia

Students begin by constructing a pedigree of the family. I give them free reign to designate gender symbols, colors, etc., for their pedigree. They are then asked to begin to evaluate patterns of inheritance. From the information given, students will be able to construct the pedigree with genotype of individuals, as shown below. In this example, I have used squares for males and circles for females. Blue people are shaded blue. If students inquire, marriage between close relatives (such as between Zach and his wife) is normally indicated with a double line. Student pedigrees may also include lineages mentioned in the story, but whose direct descent we are not following. For example, Luna and John had 13 children, which may be indicated on the pedigree, although we are only concerned with one of these offspring.

Students will then decide an inheritance pattern. Students may spend some time puzzling through this. The most satisfying explanation for inheritance pattern is that the blue phenotype is a recessive condition. Since we assume Martin was in fact blue, then he, Zach, Luna, and Ben are all “bb,” or homozygous recessive. Depending on students’ interpretation of Ben’s blueness, they may wish to designate Ben as heterozygous. (In fact, Ben’s genotype is unknown.) Elizabeth, Levy, the Ritchie girl, Alva’s mother, Alva, and Hilda are heterozygous, or “Bb.” Since Ben’s blue color reportedly faded soon after birth, some students may designate Ben’s genotype as heterozygous. If so, than Alva or Hilda (but not both) and Alva’s father could be homozygous dominant. Elizabeth’s sister, John, and Alva’s father could be homozygous dominant “BB,” or heterozygous.

Finally, students are presented with the NADH diaphorase activity graph. This graph shows how much hemoglobin is returned to normal over time. From this perspective, the heterozygous individuals look like neither of the homozygotes, but are somewhere in-between. This is a classic example of incomplete dominance.



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A transfusion was being prepared when Benjamin's grandmother spoke up. "Have you ever heard of the blue Fugates of Troublesome Creek?" she asked the doctors.

"My grandmother Luna on my dad's side was a blue Fugate. It was real bad in her," Alva Stacy, the boy's father, explained. "The doctors finally came to the conclusion that Benjamin's color was due to blood inherited from generations back."

Benjamin lost his blue tint within a few weeks, and now he is about as normal looking a seven-year-old boy as you could hope to find. His lips and fingernails still turn a shade of purple-blue when he gets cold or angry a quirk that so intrigued medical students after Benjamin's birth that they would crowd around the baby and try to make him cry. "Benjamin was a pretty big item in the hospital," his mother says with a grin.

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The odds against it were incalculable, but Martin Fugate managed to find and marry a woman who carried the same recessive gene. Elizabeth Smith, apparently, was as pale-skinned as the mountain laurel that blooms every spring around the creek hollows.

Martin and Elizabeth set up housekeeping on the banks of Troublesome and began a family. Of their seven children, four were reported to be blue.

The clan kept multiplying. Fugates married other Fugates. Sometimes they married first cousins. And they married the people who lived closest to them, the Combses, Smiths, Ritchies, and Stacys. All lived in isolation from the world, bunched in log cabins up and down the hollows, and so it was only natural that a boy married the girl next door, even if she had the same last name.

"When they settled this country back then, there was no roads. It was hard to get out, so they intermarried," says Dennis Stacy, a 51-year-old coal miner and amateur genealogist who has filled a loose-leaf notebook with the laboriously traced blood lines of several local families.

Stacy counts Fugate blood in his own veins. "If you'll notice," he observes, tracing lines on his family's chart, which lists his mother's and his father's great grandfather as Henley Fugate, "I'm kin to myself."

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Martin and Elizabeth Fugate's blue children multiplied in this natural isolation tank. The marriage of one of their blue boys, Zachariah, to his mother's sister triggered the line of succession that would result in the birth, more than 100 years later, of Benjamin Stacy.

When Benjamin was born with purple skin, his relatives told the perplexed doctors about his great grandmother Luna Fugate. One relative describes her as "blue all over," and another calls Luna "the bluest woman I ever saw."

Luna's father, Levy Fugate, was one of Zachariah Fugate's sons. Levy married a Ritchie girl and bought 200 acres of rolling land along Ball Creek. The couple had eight children, including Luna.

A fellow by the name of John E. Stacy spotted Luna at Sunday services of the Old Regular Baptist Church back before the century turned. Stacy courted her, married her, and moved over from Troublesome Creek to make a living in timber on her daddy's land.

Luna has been dead nearly 20 years now, but her widower survives. John Stacy still lives on Lick Branch of Ball Creek. His two room log cabin sits in the middle of Laurel Fork Hollow. Luna is buried at the top of the hollow. Stacy's son has built a modern house next door, but the old logger won't hear of leaving the cabin he built with timber he personally cut and hewed for Luna and their 13 children.

Stacy recalls that his father-inlaw, Levy Fugate, was "part of the family that showed blue. All them old fellers way back then was blue. One of 'em I remember seeing him when I was just a boy "Blue Anze", they called him. Most of them old people went by that name the blue Fugates. It run in that generation who lived up and down Ball [Creek]."

"They looked like anybody else, 'cept they had the blue color," Stacy says, sitting in a chair in his plaid flannel shirt and suspenders, next to a cardboard box where a small black piglet, kept as a pet, is squealing for his bottle. "I couldn't tell you what caused it."

The only thing Stacy can't or won't remember is that his wife Luna was blue. When asked ahout it, he shakes his head and stares steadfastly ahead. It would be hard to doubt this gracious man except that you can't find another person who knew Luna who doesn't remember her as being blue.

"The bluest Fugates I ever saw was Luna and her kin," says Carrie Lee Kilburn, a nurse who works at the rural medical center called Homeplace Clinic. "Luna was bluish all over. Her lips were as dark as a bruise. She was as blue a woman as I ever saw."

Luna Stacy possessed the good health common to the blue people, bearing at least 13 children before she died at 84. The clinic doctors only saw her a few times in her life and never for anything serious.

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Hilda Stacy (nee Godsey) is fiercely protective of her son. She gets upset at all the talk of inbreeding among the Fugates. One of the supermarket tabloids once sent a reporter to find out about the blue people, and she was distressed with his preoccupation with intermarriages.

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"Everyone around here knows about the blue Fugates," says Hilda Stacy who, at 26, looks more like a sister than a mother to her children. "It's common. It's nothing.''

Cawein and his colleagues published their research on hereditary diaphorase deficiency in the Archives of Internal Medicine (April, 1964) in 1964. He hasn't studied the condition for years. Even so, Cawein still gets calls for advice. One came from a blue Flugate who'd joined the Army and been sent to Panama, where his son was born bright blue. Cawein advised giving the child methylene blue and not worrying about it. Note: In this instance the reason for cyanosis was not methemoglobinemia but Rh incompatibility. This information supplied by John Graves whose uncle was the father of the child.

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 1. Cawein, Madison, et. al. "Hereditary diaphorase deficiency and methemoglobinemia". Archives of Internal Medicine, April, 1964.

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<http://www.indiana.edu/~oso/lessons/index.htm#blue>

<http://www.indiana.edu/~oso/lessons/blue.htm>

<http://www.indiana.edu/~oso/lessons/index.htm#23blue>

Modeling Inheritance: Here, we offer a means of modeling the inheritance, over many generations, of a particular allele that leads to the unusual trait of blue skin in humans. Modeling the blue people (doc) illustrates inheritance, as well as the inherent uncertainty of meiotic segregation (but not the mechanism of meiosis). It also helps make the link between genotype and phenotype, since homozygotes, who have little NADH diaphorase activity, have blue skin, while heterozygotes, who have more (but not enough) enzyme activity have blue lips and fingernails, and are blue at birth. This modeling exercise creates a pattern of individual genotypes in the classroom that can be then drawn on paper, boxed and linked with lines to create a pedigree. We also host a mirror-site for the 1982 Science 82 article by Kathy Trost on The Blue People of Troublesome Creek.

The Blue People

Over the years, there have been a number of families in which some of the individuals have blue skin. What’s going on here?

There is a human gene that codes for an enzyme called “NADH diaphorase,” which we will give the abbreviation ND. This enzyme repairs hemoglobin that has been damaged by oxidization. Humans in whom this gene is defective cannot make the ND enzyme, and accumulate damaged hemoglobin, which is blue. As a result, their skin appears blue.

In the blue families, some of the individuals are blue, some are not. How can we explain this?

Let’s model one of these families.

Martin and his wife homestead a plot of land in a fertile valley. They have kids. Over the years, a few more families settle in this valley, and the children of the several families intermarry. Many generations later, there are quite a number of people who think they might be descendents of Martin. They are quite proud of this, because legend says that he was blue.

To model what happens in this valley, let’s follow the genetic inheritance of Martin’s descendents. Martin was blue, so he must not have had a functional copy of the ND gene. We can model this by representing Martin with two blue pieces of yarn—one of each of Martin’s ND genes. Martin’s wife was unrelated to him, and had two functional ND genes, so we can represent her with two white pieces of yarn. Let's put two blue pieces of yarn on a desk at the back of the room to represent Martin, and two pieces of white yarn on the desk next to it to represent his wife.

The way genetics works, we each have two sets of genes, one set from Mom, one set from Dad. Martin’s children, therefore, received one blue gene from Martin, and one white gene from his wife. We can represent Martin’s children with one blue piece of yarn, and one white piece of yarn. Let’s consider only two of Martin’s children, William and Hanna, to keep things simple. To represent William, let's put a blue piece of yarn (from Martin) and a white piece of yarn (from Martin's wife) on a desk in front of the desks representing Martin and his wife. To represent Hanna, let's put a blue and a white piece of yarn on another desk in the same row.

Are William and Hanna blue? Think about it and discuss it. They have one non-functional gene from Martin (blue yarn), but they have a perfectly good gene from Martin’s wife (white yarn). If the perfectly good, functional gene can make the ND enzyme, can they repair damaged hemoglobin?

Now, William and Hanna grow up and marry newcomers to the valley. We can model William’s wife with two white pieces of yarn and Hanna’s husband with two white pieces of yarn. Let's put pieces of yarn on two more desks to represent the people whom William and Hanna marry.

From these marriages, William has several children and Hanna has several children. How can we represent these children? William’s children each inherit a “white” gene from William’s wife, which we can represent with a piece of white yarn. Each of the children must also inherit a gene from William—but which one? To make the choice, flip a coin. If it comes up heads, give the child a white piece of yarn. If it comes out tails, give the child a blue piece of yarn. Represent these children with the appropriate pieces of yarn on desks in a new row.

We can do the same for Hanna’s children. Each has one white piece of yarn, and a second piece of yarn that is determined by the flip of the coin.

Why do we use a coin flip? Think about it and discuss it. The answer, quite simply, is that neither Hanna nor William can decide which gene to put into a particular egg cell or sperm cell. That choice is not up to them, and occurs entirely at random.

If you like, you can follow this family through the generations, each time having the children inherit one ND gene from each parent. As long as each of Martin’s descendents marries someone from a different family, the blue ND gene will always be paired with a white one.

But, what if one of Martin’s descendents marries another of his descendents? Let’s model this by allowing marriages between Hanna’s children and William’s children. These would be marriages between cousins, which has been known to occur, especially in small villages in isolated areas.

The most interesting thing occurs if one of Hanna’s children, represented by blue and white yarn, marries one of William’s children, also represented by blue and white yarn. It this occurs, what will their children be like? For each child, we need to determine whether the child inherits the white or the blue gene from Mom, and whether the child inherits the white or the blue gene from Dad. Model this family—give them 10 children. Do any of them happen to inherit blue genes from both Mom and Dad? If they do, then they are blue, just like Martin was.

Now consider what happens over many generations. Martin’s blue gene, represented by the blue yarn, is passed on from generation to generation. It may not get passed on in every lineage, if the luck-of-the-coin-flip works out just right, but most likely it moves through the generations. Usually, it is paired with a white gene. But sometimes there may be a great-great-great-great grandchild of Martin’s who marries another great-great-great-great grandchild of his, and the blue trait may show up again.

In actual fact, this is what has happened in the Blue Families. As you will see when you read The Blue People of Troublesome Creek, there is a simple cure for blueness, so this trait is no longer troublesome. You will also see that the individuals we have represented with blue and white yarn are not entirely free of blueness—they are bluer than normal at birth, but “pinken up” quickly, and their lips and fingernails can be somewhat blue. The message from Ben Stacy tells us this. What is the value, to you, of the blue people and the bits of yarn? They should help you see how inheritance works, and how our traits are determined by genes and chemistry. It sometimes helps to know that real people, in real families, have helped us learn how it works.

THE BLUE PEOPLE OF TROUBLESOME CREEK

The story of an Appalachian malady, an inquisitive doctor, and a paradoxical cure.

by Cathy Trost

©Science 82, November, 1982

Six generations after a French orphan named Martin Fugate settled on the banks of eastern Kentucky's Troublesome Creek with his redheaded American bride, his great-great-great great grandson was born in a modern hospital not far from where the creek still runs.

The boy inherited his father's lankiness and his mother's slightly nasal way of speaking.

What he got from Martin Fugate was dark blue skin. "It was almost purple," his father recalls.

Doctors were so astonished by the color of Benjy Stacy's skin that they raced him by ambulance from the maternity ward in the hospital near Hazard to a medical clinic in Lexington. Two days of tests produced no explanation for skin the color of a bruised plum.

A transfusion was being prepared when Benjy's grandmother spoke up. "Have you ever heard of the blue Fugates of Troublesome Creek?" she asked the doctors.

"My grandmother Luna on my dad's side was a blue Fugate. It was real bad in her," Alva Stacy, the boy's father, explained. "The doctors finally came to the conclusion that Benjy's color was due to blood inherited from generations back."

Benjy lost his blue tint within a few weeks, and now he is about as normal looking a seven-year-old boy as you could hope to find. His lips and fingernails still turn a shade of purple-blue when he gets cold or angry a quirk that so intrigued medical students after Benjy's birth that they would crowd around the baby and try to make him cry. "Benjy was a pretty big item in the hospital," his mother says with a grin.

Dark blue lips and fingernails are the only traces of Martin Fugate's legacy left in the boy; that, and the recessive gene that has shaded many of the Fugates and their kin blue for the past 162 years.

They're known simply as the "blue people" in the hills and hollows around Troublesome and Ball Creeks. Most lived to their 80s and 90s without serious illness associated with the skin discoloration. For some, though, there was a pain not seen in lab tests. That was the pain of being blue in a world that is mostly shades of white to black.

There was always speculation in the hollows about what made the blue people blue: heart disease, a lung disorder, the possibility proposed by one old-timer that "their blood is just a little closer to their skin." But no one knew for sure, and doctors rarely paid visits to the remote creekside settlements where most of the "blue Fugates" lived until well into the 1950s. By the time a young hematologist from the University of Kentucky came down to Troublesome Creek in the 1960s to cure the blue people, Martin Fugate's descendants had multiplied their recessive genes all over the Cumberland Plateau.

Madison Cawein began hearing rumors about the blue people when he went to work at the University of Kentucky's Lexington medical clinic in 1960. "I'm a hematologist, so something like that perks up my ears," Cawein says, sipping on whiskey sours and letting his mind slip back to the summer he spent "tromping around the hills looking for blue people."

Cawein is no stranger to eccentricities of the body. He helped isolate an antidote for cholera, and he did some of the early work on L-dopa, the drug for Parkinson's disease. But his first love, which he developed as an Army medical technician in World War II, was hematology. "Blood cells always looked so beautiful to me," he says.

Cawein would drive back and forth between Lexington and Hazard an eight-hour ordeal before the tollway was built and scour the hills looking for the blue people he'd heard rumors about. The American Heart Association had a clinic in Hazard, and it was there that Cawein met "a great big nurse" who offered to help.

Her name was Ruth Pendergrass, and she had been trying to stir up medical interest in the blue people ever since a dark blue woman walked into the county health department one bitterly cold afternoon and asked for a blood test.

"She had been out in the cold and she was just blue!" recalls Pendergrass, who is now 69 and retired from nursing. "Her face and her fingernails were almost indigo blue. It like to scared me to death! She looked like she was having a heart attack. I just knew that patient was going to die right there in the health department, but she wasn't a'tall alarmed. She told me that her family was the blue Combses who lived up on Ball Creek. She was a sister to one of the Fugate women." About this same time, another of the blue Combses, named Luke, had taken his sick wife up to the clinic at Lexington. One look at Luke was enough to "get those doctors down here in a hurry," says Pendergrass, who joined Cawein to look for more blue people.

Trudging up and down the hollows, fending off "the two mean dogs that everyone had in their front yard," the doctor and the nurse would spot someone at the top of a hill who looked blue and take off in wild pursuit. By the time they'd get to the top, the person would be gone. Finally, one day when the frustrated doctor was idling inside the Hazard clinic, Patrick and Rachel Ritchie walked in.

"They were bluer'n hell," Cawein says. "Well, as you can imagine, I really examined them. After concluding that there was no evidence of heart disease, I said 'Aha!' I started asking them questions: 'Do you have any relatives who are blue?' then I sat down and we began to chart the family."

Cawein remembers the pain that showed on the Ritchie brother's and sister's faces. "They were really embarrassed about being blue," he said. "Patrick was all hunched down in the hall. Rachel was leaning against the wall. They wouldn't come into the waiting room. You could tell how much it bothered them to be blue."

After ruling out heart and lung diseases, the doctor suspected methemoglobinemia, a rare hereditary blood disorder that results from excess levels of methemoglobin in the blood. Methemoglobin which is blue, is a nonfunctional form of the red hemoglobin that carries oxygen. It is the color of oxygen-depleted blood seen in the blue veins just below the skin.

If the blue people did have methemoglobinemia, the next step was to find out the cause. It can be brought on by several things: abnormal hemoglobin formation, an enzyme deficiency, and taking too much of certain drugs, including vitamin K, which is essential for blood clotting and is abundant in pork liver and vegetable oil.

Cawein drew "lots of blood" from the Ritchies and hurried back to his lab. He tested first for abnormal hemoglobin, but the results were negative.

Stumped, the doctor turned to the medical literature for a clue. He found references to methemoglobinemia dating to the turn of the century, but it wasn't until he came across E. M. Scott's 1960 report in the Journal of Clinical Investigation (vol. 39, 1960) that the answer began to emerge.

Scott was a Public Health Service doctor at the Arctic Health Research Center in Anchorage who had discovered hereditary methemoglobinemia among Alaskan Eskimos and Indians. It was caused, Scott speculated, by an absence of the enzyme diaphorase from their red blood cells. In normal people hemoglobin is converted to methemoglobin at a very slow rate. If this conversion continued, all the body's hemoglobin would eventually be rendered useless. Normally diaphorase converts methemoglobin back to hemoglobin. Scott also concluded that the condition was inherited as a simple recessive trait. In other words, to get the disorder, a person would have to inherit two genes for it, one from each parent. Somebody with only one gene would not have the condition but could pass the gene to a child.

Scott's Alaskans seemed to match Cawein's blue people. If the condition were inherited as a recessive trait, it would appear most often in an inbred line.

Cawein needed fresh blood to do an enzyme assay. He had to drive eight hours back to Hazard to search out the Ritchies, who lived in a tapped-out mining town called Hardburly. They took the doctor to see their uncle, who was blue, too. While in the hills, Cawein drove over to see Zach (Big Man) Fugate, the 76-year-old patriarch of the clan on Troublesome Creek. His car gave out on the dirt road to Zach's house, and the doctor had to borrow a Jeep from a filling station.

Zach took the doctor even farther up Copperhead Hollow to see his Aunt Bessie Fugate, who was blue. Bessie had an iron pot of clothes boiling in her front yard, but she graciously allowed the doctor to draw some of her blood.

"So I brought back the new blood and set up my enzyme assay," Cawein continued. "And by God, they didn't have the enzyme diaphorase. I looked at other enzymes and nothing was wrong with them. So I knew we had the defect defined.''

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and some Fugate family Bibles listing ancestors, Cawein has constructed a fairly complete story.[see inferred Pedigree on right; more accurate pedigree below]

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Pedigree of Methemoglobinemia

Pedigree information graciously provided by Mary D. Fugate, publisher of The

Fugate Family Newsletter.

Curing the Kentucky Blues

Dr. Madison Cawein was a hematologist at the University of Kentucky Medical Center when he heard stories about the blue people of Troublesome Creek. He scoured the area around Hazard, Kentucky, trying to find the blue people but to no avail until Patrick and Rachel Ritchie, a brother and sister and both blue, walked into the Hazard clinic on a day when Cawein was there. He checked to make sure the siblings had no heart problems and then he began asking about their families and other blue people. He had found the descendants of Martin Fugate.

Dr. Cawein drew blood and eventually demonstrated that the problem was a deficiency of NADH diaphorase. He went out into the hills and found other blue people including Zach Fugate and his Aunt Bessie Fugate all living near a nearly dead mining town known as Hardburly.

The doctor had noticed that the blue people were not particularly happy about being blue. So, he hit upon a particularly brilliant scheme to help them. He knew that a second enzyme could do the trick if a good reducing agent was present. So, he injected Patrick and Rachel with methylene blue and within a few minutes, they both turned pink! They were delighted. The change was only transient but he left them some methylene blue pills to take on a daily basis and it worked. In fact, the mountain people could see the blue leaving their bodies since some of the methylene blue was excreted in their urine. One of the older mountain men confided to Dr. Cawein, "I can see that old blue running out of my skin."

The doctor never did reveal the location of the blue people and what with a daily dose of methylene blue, it may be that no one will ever find them again.

Curing the Blues in Ireland

adapted from Am. J. Haem 42: 3-6, 1993

Prior to WWII, Dr. Deeny practiced medicine in Bainbridge, Ireland, a town of about 5,000. He was sure that he could treat the cyanosis associated with heart failure by dosing the patients with a reducing agent such as ascorbic acid.

One morning in his office, he saw outside a deeply cyanosed man walk by! Unable to get outside to stop the man, he went to the local police station and asked if they knew of a blue man in the locality. Dr. Deeny was told there were two, blue men! "Fred and Russell, brothers you know." Deeny had not know about them because the brothers were Protestant while Deeny was Catholic.

He called on the brothers and asked if they would like to be pink. They agreed to his experiment. So, Dr. Deeny did a controlled experiment and gave one brother a daily dose of ascorbic acid (vitamin C) while the other received a placebo. The treated brother turned pink while the control remained blue.

The Chemistry and Genetics

The Blue Families carry an ineffective allele of the gene for NADH Diaphorase. NADH Diaphorase is an enzyme that repairs hemoglobin when it has been damaged by oxidation, leaving the iron atom in the +3 state. However, if the enzyme is inactive due to DNA sequence variation, then damaged hemoglobin cannot be repaired, and accumulates--producing blue skin color.

Dr. Cawein, of The Blue People of Troublesome Creek and Curing the Kentucky Blues, used methylene blue to repair the damaged hemoglobin. That is, methylene blue, in its reduced form, is a colorless, water-solulble molecule. When it has been oxidized, it becomes blue. The blue tint that this gives to urine accounts for the last quote in Kathy Trost's article, that "I can see that old blue running out of my skin." The use of vitamin C by Dr. Deeny in Ireland achieves the same result of repairing damaged hemoglobin. However, vitamin C is colorless, so there is no excretion of blue pigment.

The blue trait is a good example of something that does not fit the traditional view of alleles as being dominant or recessive. A person carrying one copy of the "blue allele" of ND has more total ND enzyme than does a person carrying two copies of the"blue allele," and thus the blue characteristics are much less pronounced; the "blue allele" is recessive. But the blue characteristics are not altogether absent (note the blueness at birth, and the blueness of lips and fingernails), so this allele does not fit the typical definition of "recessive." In fact, most genetic variation reflects alleles that are neither strictly dominant nor strictly recessive; gradations, such as that we see here, are the norm.