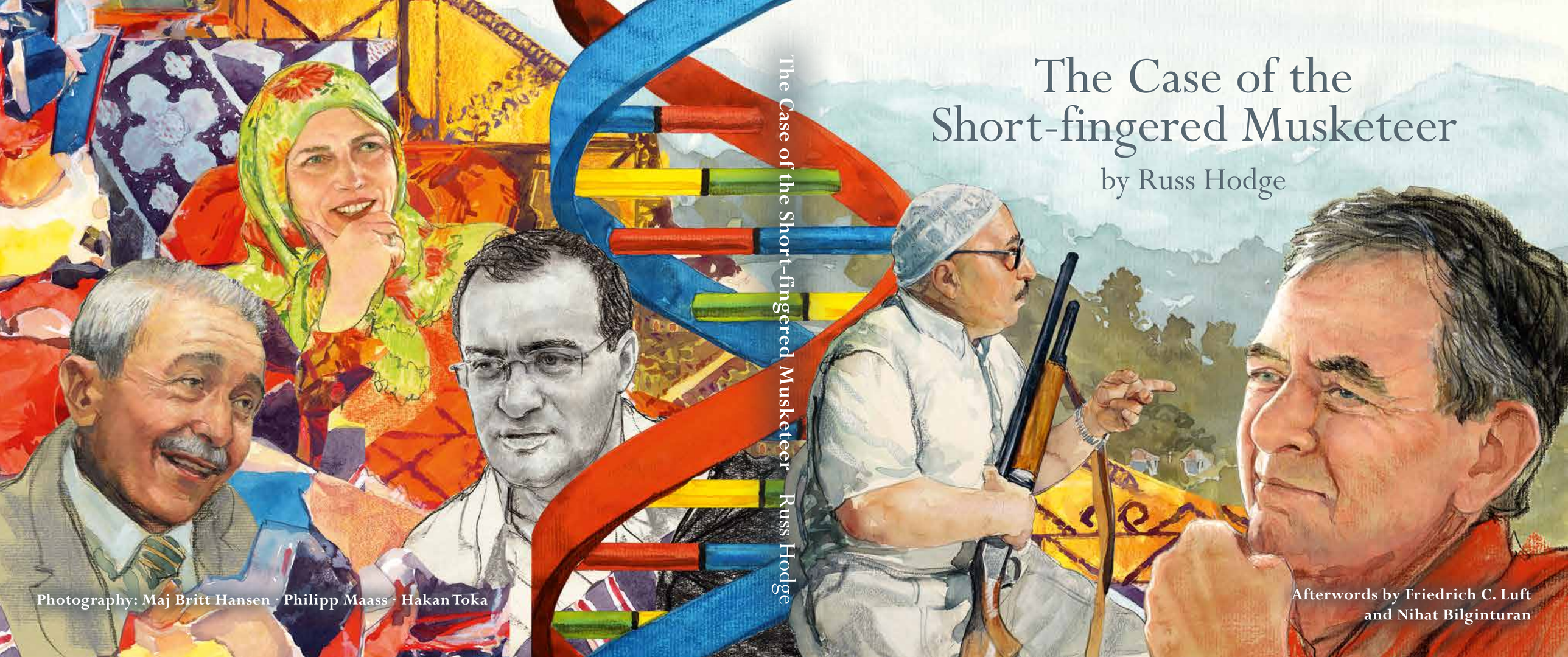

The Case of the Short-fingered Musketeer

by Russ Hodge

Photography: Maj Britt Hansen · Philipp Maass · Hakan Toka

Afterwords by Friedrich C. Luft and Nihat Bilginturan

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The Case of the Short-fingered Musketeer

a biomedical adventure

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afterwords by Friedrich C. Luft
and Nihat Bilginturan

photographs: Maj Britt Hansen, Philipp Maass, Hakan Toka
design: Nicola Graf
cover painting: Stephen Johnson

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The Case of the Short-fingered Musketeer

Dedication

This book is dedicated to my family: Gabi Krietemeyer, Jesper Hodge, Sharon Hodge, and Lisa Hodge, who have made so many sacrifices so that it could be written, and to my parents, Ed and Jo Hodge.

Acknowledgements

Writing this book has been a tremendously challenging experience. Every time this crazy project threatened to flounder and crash on the rocks, someone stepped in at just the right moment to save the day. There are too many to thank individually here, but several people deserve special mention for going far beyond the call of duty and averting many very near disasters:

First and foremost, Fred Luft, who has been just as inspirational to me as he has been to his many students and colleagues over the years, has been supportive in every way, and has shown amazing patience with the writing and the writer;

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Okan Toka, whose amazing year on the Black Sea coast convinced me right from the beginning that there was a book in this story; Okan always came through at just the right moment to help (and we're waiting for your book, too);

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Former MDC Scientific Director Walter Birchmeier, who initially gave the project a green light and is responsible for my position at the MDC, and current Director Walter Rosenthal, who has enthusiastically supported the work along the way;

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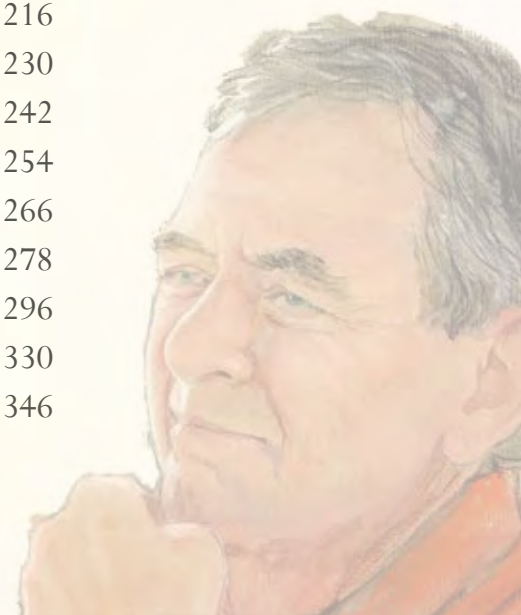
My good Berlin friends Małgorzata Elszyn and Ugur Harputluoglu, who have been supportive in so many ways;

And, as always, thanks to Rainer Bender, Ingrid André, Paul Bühl, and all their colleagues at ColorDruck Leimen for their excellent advice and work in printing this book;

And last but certainly not least, the villagers of "Karamat", who truly are among the most hospitable people on the planet, who welcomed a writer just as warmly as they have welcomed doctors and scientists for so many years – may they live long, healthy, and peaceful lives.

The Case of the Short-Fingered Musketeer

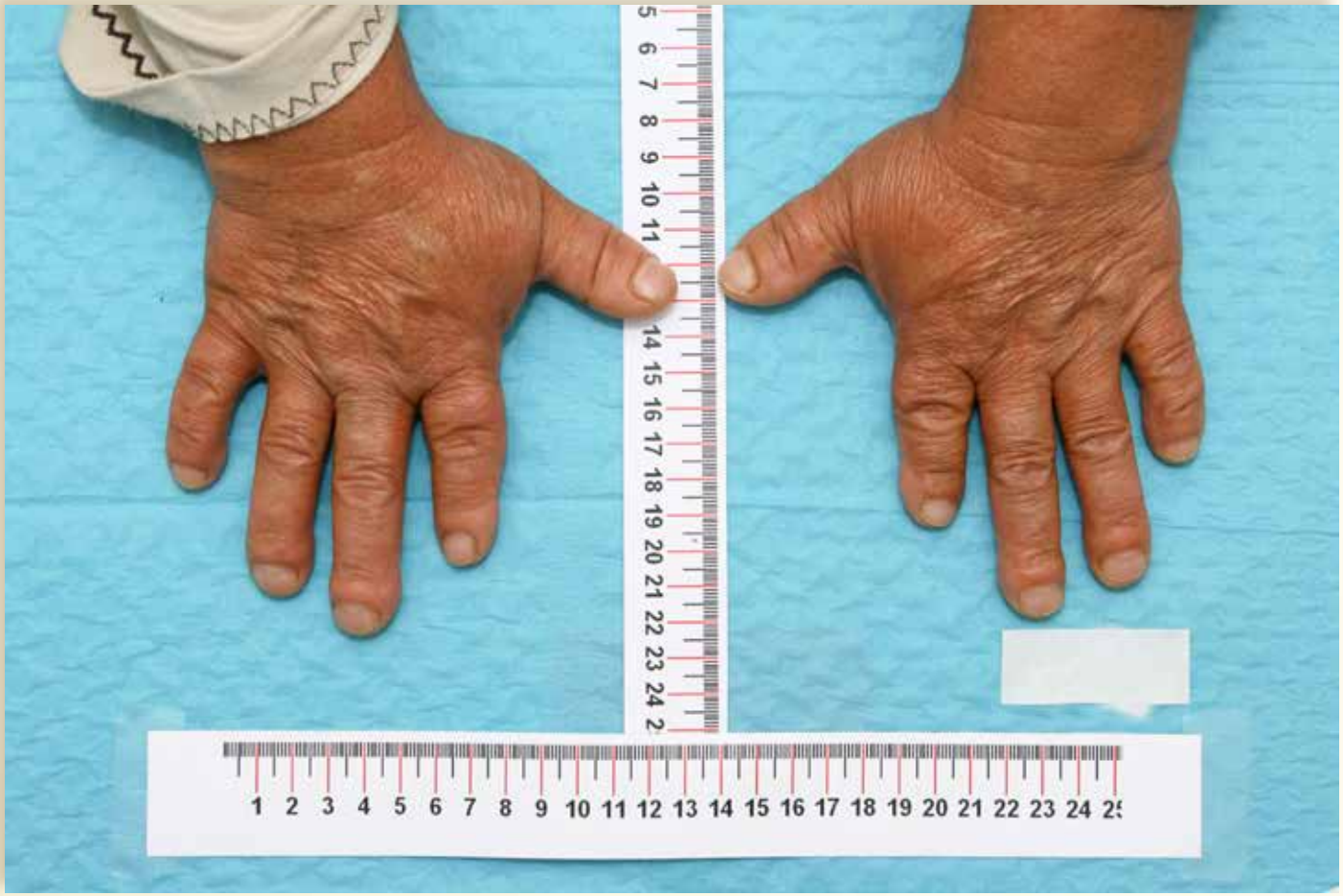


Introduction

This is the story of a group of researchers searching for the causes of one of mankind's most deadly diseases. It is simultaneously the story of a Turkish family with a unique hereditary condition. A defect in their DNA gives them short fingers and toes, which is trivial, but also gives them extraordinarily high blood pressure that brings sudden death at an early age. Fifty years ago a family member set off to find a doctor who could shed light on his family's health problems. In doing so, he touched off a biomedical drama that has reached across the world and shed new light on the relationship between information in our DNA and disease.

Most science stories revolve around a mystery, and this tale has more elements of that genre than most: multiple deaths, a quest for answers that has lasted more than 50 years, a cast of characters colorful to the point of eccentricity, and the application of cutting-edge technology to a sophisticated puzzle. Appropriately enough, there were a few incidents involving firearms. And – almost – a prison break.

Over a century ago, sudden death began disrupting the peaceful existence of a family of farmers living on the Black Sea coast. Initially its selection of victims seemed random. But in the early 1960s, the family noticed a pattern and sought the help of scientists in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discovering its causes. Thirty years later, a physician and researcher named Fred Luft sank his teeth into the story and – like the best literary detectives – refused to let go. At the time he had no idea that the project might one day reveal a new mechanism by which disease arises in our cells and bodies. Or that it would require two decades to find.

It hasn't been easy going. Despite continual revolutions in biotechnology and scientists' understanding of the roles that genes play in health and disease, the answer to the puzzle has remined elusive. The lab has thrown nearly every new method and technology at the problem, but it always seems to dance away again, teasing them along. Anyone sensible would have been forgiven for abandoning the project long ago. That surely would have happened without an unusual amount of persistence on the part of the scientists and extraordinary efforts on the part of the family in Turkey. So this is a story about the human side of research: in particular about a man who has continued to inspire and motivate colleagues and students despite opportunities for frustration at every turn.

The case is a "what-dunnit" rather than a "who-dunnit," with ripe pickings for a storyteller. In the early years, it was cited as an exceptional attempt at what is now called "molecular medicine." But there has never been any guarantee that the ultimate answer to the riddle would be very meaningful or interesting. And three years ago, when the research for this book began, a definitive answer to the family's health problems was still missing, which made it a mystery story without a final chapter.

As this book appears, however, the situation is rapidly changing through a paper just published by Fred's lab in the *Journal of Clinical Investigation* and another that the group is about to submit for publication soon. The story that has appeared involves a related case and doesn't, therefore, answer every question – making this more like a real-life crime story than a literary one. Despite the loose ends, the new study brings a satisfying conclusion to this edition of the book. Soon there will need to be an updated final chapter, and maybe more than one. Finally, the case is breaking open.

Even without such a temporary resolution, the story is an apt parable for the last half-century of biomedical research. In the early 1960s, as a Turkish Imam set out to find a reason for his family's health problems, James Watson and Francis Crick were setting off for Sweden to receive a Nobel Prize. With the discovery of the structure of DNA, they had solved an age-old mystery by identifying the substance that genes were made of. Their work contributed to an explosion of new kinds of biotechnology, and just about all of it has, in some way or other, been applied to the family's strange condition. Until now, these attempts have raised more questions than answers. Yet Fred Luft's lab has persistently followed the story wherever it might lead, and in doing so, the group has acquired the reputation of mavericks.

Part of their motivation lies with the fact that hypertension, or high blood pressure, is one of mankind's greatest silent killers. It has a hydra-like nature that rears its head in many tissues, across the body as a whole. Once things get rolling, one organ system crashes after another. Finding causes for such ailments inevitably requires looking at humans in a holistic way, as extraordinarily complex systems that cover a spectrum of scale from tiny molecules to our bodies as a whole, but limitations in technology and other factors have made it impossible to truly link these levels. Imagine trying to conduct a stakeout of a house using only a microscope and the Hubble space telescope, and you'll get the idea. The biomedical equivalent of a pair of binoculars, covering the mid-range, has been missing.

For decades, scientists have known that inheriting particular forms of genes can increase the risk that a person

Fred Luft

will develop hypertension and many other diseases. In some cases the genes remain enigmas; finding them often requires looking in the most unlikely places. In this case, the place has been a family of Turkish farmers who have inherited at least two unusual and seemingly unconnected traits.

I first heard of the short-fingered musketeer in Fred Luft's office in a clinic in a suburb of Berlin, amidst neatly stacked journal articles, printouts of experimental data, and other artifacts of active research. Fred, a German-American, is a physician and a specialist in nephrology and cardiovascular disease.

I had come intending to write an article about his research activities. The week before he had sent me a few papers about a project to find genes linked to high blood pressure. At first glance the work resembled other studies of human genetics going on across the globe. There was no hint that it would take me to a distant country and become a personal adventure. Fred, on the other hand, might have predicted it – the same thing has happened to everyone else connected to the project. They all say two things: that Fred is a remarkable scientist and teacher, and that taking part in this project has had a huge impact on their lives.

Fred first heard the story 20 years ago from a colleague who had come across an obscure paper in the medical literature. That article had been written in the 1970s by a Turkish pediatric physician and geneticist named Nihat Bilginturan. He, in turn, had learned of the case from a family that appeared on his hospital ward one day with a curious tale. They were farmers from Northern Turkey, and they had the story first-hand – they were living it. A mysterious ailment was picking them off, unexpectedly, just as they reached middle age.

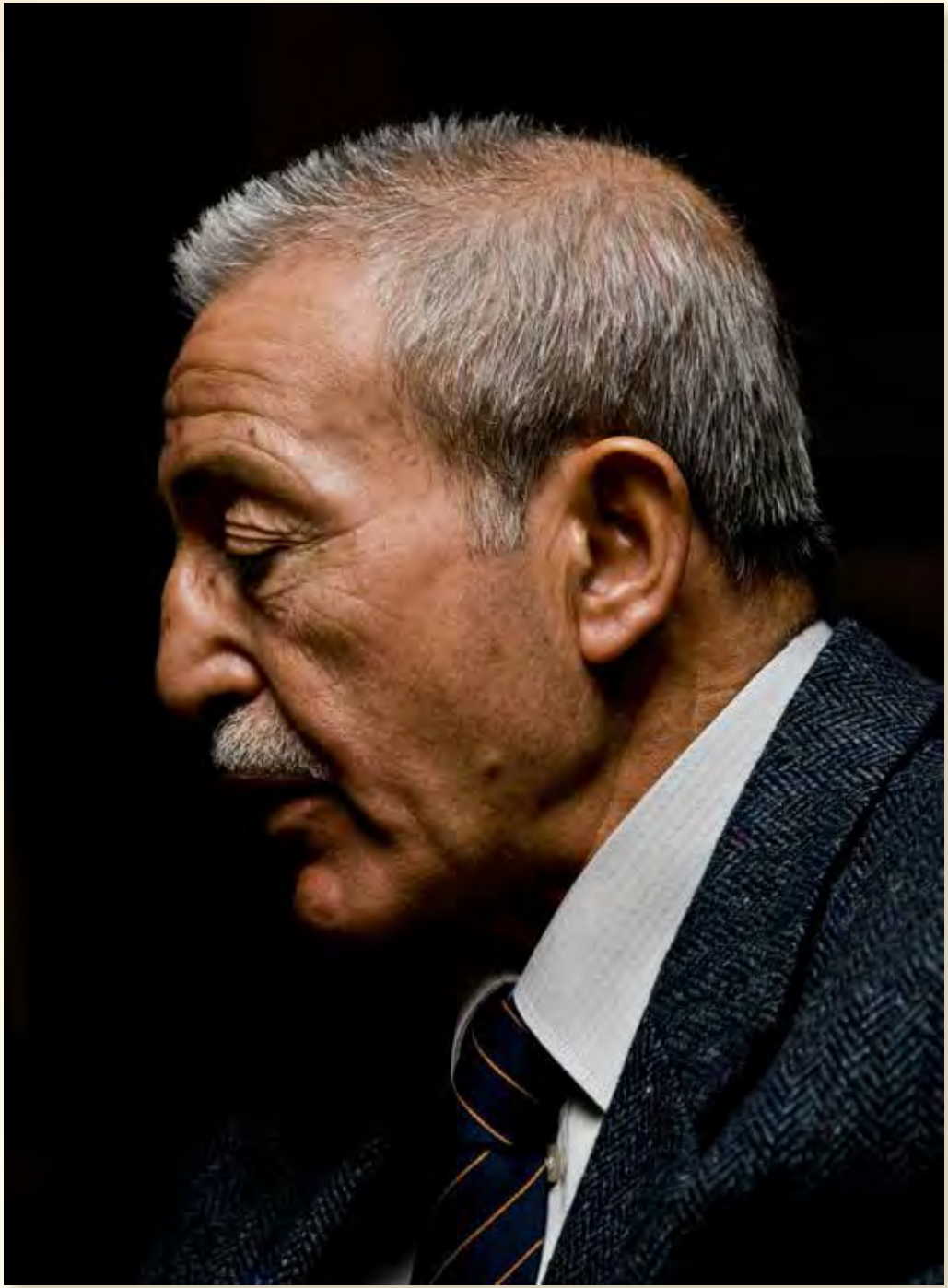
Most studies of genetic disease take place in the sterile environment of laboratories where researchers encounter patients only as bits of tissue, or as anonymous, numbered codes on test tubes and cell cultures. Fred decided to do things differently: to find the Turkish family, visit them, and enlist their direct help. In return, he could offer them medical care.

This formed the basis of a deep personal relationship between scientists and their subjects that has made all the difference. For twenty years the family has submitted to poking and prodding, welcoming foreign researchers with open arms, allowing their homes to be turned into makeshift hospitals. Several of them have been brought to Berlin – a great adventure for people who had, for the most part, never been in an airplane or traveled more than a few kilometers from their village. The story is as much theirs as that of the scientists, and this book attempts to reflect that.

Every day's headlines announce the discovery of new links between genes and disease; they rarely depict the much deeper, underlying drama of encounters between physicians, their patients, and research laboratories. Most of the stories that make the news begin in the laboratory and eventually move to the clinic. Trying to do things the other way around – starting with the patients themselves – is much, much harder. So far, it has rarely met with success.

In such cases, it is devilishly difficult to pin down even the causes of a genetic disease. Given our current state of knowledge and technology, finding a potential cure seems almost miraculous. Amazingly enough, at one point in this story it seemed to have happened. Then Fred and his colleagues faced a great ethical dilemma that has never completely left their minds.

"A potential surgical cure exists for this condition, which has not been tested in these patients," Fred says. "Could such a treatment help affected persons, and how



Nihat Bilginturan

can we be certain? We all agree that first, the molecular mechanism that underlies the disease must be understood. Then we will make therapeutic assessments and recommendations."

Even without a possible cure, molecular medicine has already had a huge payoff that has been largely overlooked by the media. A clear diagnosis of a person's ailment may permit a treatment already available in the medical arsenal. That, too, has happened here – Fred's original decision to seek out the family has already saved many, many lives. Even so, his actions were the result of the journey that one of them took, long ago, to seek help.

Research into the causes of genetic diseases usually requires crossing boundaries between disciplines such as biology, chemistry, physics, and computer science – and cultural boundaries such as language, religion, and health care systems. Yet the greatest obstacle is perhaps the gap that remains between molecular biology and medicine, whose practitioners are trained in different ways, taught to think differently, and are pushed into different lifestyles. Whatever the future brings for molecular medicine, it will probably require a new generation of physician/scientist who is equally at home in both cultures. Which is why Fred Luft has devoted a great deal of his career to bringing young scientists and physicians back and forth across the boundaries.

This book is the product of dozens of hours of interviews carried out in Germany and Turkey with its major figures, including nearly all the scientists and many members of the family in Turkey. The researchers provided a rare glimpse behind the scenes of their laboratory: debates about the meaning of results and what to do next, hypotheses that led nowhere, politics, and the quirks of personalities. Most of these aspects of science never appear in a published paper. It's a bit like wandering backstage in an opera house and attending dress rehearsals before the curtain goes up on a big premiere.

In Turkey our hosts talked openly about their lives and thoughts – including discussions of religion and the problems that face their country. The family's children shared their poems, songs, and intimate dreams. "My life is so exciting I could write a whole novel about it," said one fifteen-year-old girl who goes to school in a larger town, but has never traveled more than 50 kilometers from home. I had no trouble believing her.

I have tried to recount the events as faithfully as possible, with constant assistance and comments from the figures who appear in the book. Direct witnesses have helped fill in the early parts of the story. I have made only one important change: the names and the precise location of the families who so graciously welcomed us into their lives.

The people affected by *Bilginturan's syndrome*, as the condition is now called, do not regard themselves as unusual or sick, and they should not be seen as curiosities. The discovery that their short fingers and high blood pressure are caused by a genetic defect has not stigmatized their society or made them oversensitive to differences between affected and nonaffected family members. In fact, now that their lives have been extended thanks to new drugs for treating hypertension, the disease has not shaken their lives in any major way. Except for the occasional disruptions caused by doctors and scientists whom they have come to know and trust. That could change if they were to be tracked down and made into spectacles by the media, or even if they were regarded merely as anonymous subjects in a scientific project.

Many of us who visited Northern Turkey in the context of this study have been moved by even a very short exposure to the family's way of life – a harmonious blend of nature, hard work, and religion. During the trip we had to confront and reexamine preconceptions that had

been shaped by the Western media. Very few Europeans or Americans have witnessed these societies from the inside, or heard what they have to say about the way their religion is being warped to fit political or ideological agendas. This book is not about politics or the way religion figures into world conflicts, but from time to time such themes have reared their heads, even in the course of a scientific study.

The visits to the Black Sea have been stirring personal experiences for me and every scientist who has made the trip. As a young postdoc named Philipp Maass put it, "I've spent years at a lab bench working on this kind of project in a completely abstract way. Meeting affected people and their families gives you a completely different perspective on the meaning of this type of research. The people are no longer just anonymous numbers in statistical studies, or labels on test tubes." Philipp is also a talented photographer who took many of the pictures in this book.

And then there is Okan Toka, a young doctor who grew up in Germany as the son of Turkish parents. Okan is one of the main figures of the story: Thirteen years ago, as he was looking for a thesis topic, Fred Luft convinced him to spend a year on the Black Sea to carry out a complex drug trial. The goal was to search for medications that would extend the lives of affected family members. It would be a chance for Okan to explore his roots, Fred said, and a once-in-a-lifetime experience that would be invaluable as he completed his medical training.

That prediction was more than fulfilled. Okan's adventures during his year have had a deep impact on his life. And they play a central role in this book – among other things, they inspired the title. One of Okan's patients fired an old musket, setting off a chain of events that threatened both the success of the study and the old man's life.

Since his return to Germany, Okan has spent years tirelessly collecting hypertension drugs, mostly donated by pharmaceutical companies, and getting them to the family. Few of them have medical insurance or any consistent access to medical care, so this has extended many lives.

In closure, a personal comment: It is difficult to write such a book with the distance necessary to judge the objective value of a scientific project. Many other laboratories are carrying out research into hypertension. Any of them might be the source of a breakthrough in understanding the disease. But following the story of this group captures a special moment in science, a time when our view of human health is undergoing a rapid and dramatic evolution.

We know that something is missing in molecular medicine; we still lack ideas and technologies that will allow researchers and physicians to cross the threshold from recognizing such diseases to more easily understanding their causes, treating them, and perhaps preventing them in the first place. That moment will come. It's tempting to think that the elements needed to make it happen may already be around, in some form; they may even be scattered throughout this book, like the clues to a mystery story that have so far gone unrecognized.

That has happened before in the history of science writing. *The Voyage of the Beagle*, written two decades before Charles Darwin published *The Origin of Species*, provides deep insights into the way naturalists regarded the world just before everything changed. A close reading of that work shows how all the evidence for evolution lay plainly at hand; what was missing was the powerful, integrative concept needed to draw them all together.

Only in finishing this book did I realize what is probably its central message. We live in a rapidly changing

world that has been accompanied by immense social problems. In science, this process is greatly accelerated. In the West, there has been time to integrate both types of change. Our hosts in Turkey have experienced them in a vastly accelerated form, within the space of a single generation. In this case, scientists and doctors have become important in bridging gaps of culture, technology, and health. They have done so with an unusual sense of the obligation that comes with their work – and have assumed a long-term responsibility for the family's health.

Ultimately this project – or similar ones taking place across the globe – may well lead to principles that explain hypertension and other major diseases that affect people everywhere. In the same way, the family's small hands are a symbol for something larger. You only have to take one into your own, in a clasp of friendship, to see it as a thing of beauty, an example of the wonderful diversity of our species. It is too easy to dismiss what is unusual – whether short fingers or a scarf on a woman's head – as strange and divisive, something to categorize people into "us" and "them". A deeper look reveals that such differences are to be treasured, and if we are open to them, we can learn a great deal about how to live together in a quickly changing world.

Russ Hodge, October, 2012

1 A death in the family

By mid-afternoon the fog was flowing in from the sea, first as long wisps that snaked into the valleys, then steadily rising into the hills like a rumpled white blanket. It had not yet reached the crooked road where a group of people shuffled through the dust and heat toward the cemetery. From the slope above, stalks of corn cast thin shadows across the plain wooden box that held the body. The men who carried it had a precarious job. The gravel road was littered with fist-sized rocks and pitted with treacherous holes, and on one side it dropped off into a deep ravine. Parents held the hands of their children so they wouldn't fall over the edge. The youngest ones didn't quite understand what was going on but sensed something heavy and solemn that you didn't dare interrupt with any nonsense.

The cemetery lay in a small, fenced-off plot of land at the bottom of a hill, tucked between fields of corn that were lush and green and ready for harvest. An old man opened the gate for the men bearing the body. Then came the relatives – the men in dark suits, women with their heads wrapped in scarves – and neighbors who had come directly from their farms, still in their work clothes.

The graves were marked with simple, white headstones that glowed against the grass. A new hole had been dug to receive the body. Beside it stood Kemal, the *Hoca*, or religious leader of the village.

As he waited for the mourners to gather, he struggled to keep his mind on the matter at hand. His thoughts on that day 50 years ago have become a legend in his family because they prompted him to do something that has profoundly influenced their lives ever since.

His main distraction wasn't that they were burying his uncle. Three days earlier his aunt had gone to wake Mehmet in the morning, only to find his skin cold. He had died in his sleep, completely unexpectedly; a few hours earlier he had been out in front of the house, complaining about the weather and the state of the corn. Upon receiving the news, Kemal and his brothers went to the house for the ceremony of preparing the body. Custom dictated that Mehmet be disrobed, stripped even of his wedding ring, then washed and wrapped from head to foot in a white shroud. After hushed visits by family members and friends, the body was placed in a simple coffin to be carried down the hill.

Nor was Kemal preoccupied with the business that often came in the wake of a funeral – at least not yet. The unexpected death left behind a wife and four children and unsettled affairs. The fields had to be divided up among the heirs, often a tricky problem that required help from the community's religious leader. The negotiations were precarious because a decision would affect the families for generations.

Still, these concerns paled in comparison to that other thing. Kemal was a scholar with a magnificent mind. Through Mehmet's death, he had suddenly perceived a pattern, like the intricate phrases of the Qu'ran that he had learned by heart. He could name a dozen others who had died unexpectedly, at an early age.

Kemal's father Cemal, gone for ten years now, had barely reached his fifties. Now his uncle Mehmet had been struck down precisely the same way. Their neighbors lived longer, long enough to watch their grandchildren grow and romp up and down the hills. They died of diseases, or accidents, or simply because they were old, but they didn't fall down in their fields in the prime of life. Nor simply go to sleep and fail to rise in the morning without any warning.

Well – perhaps not completely without warning. Mehmet had complained of dizzy spells, and after a day of work his face often turned red and his hands quivered. Kemal normally felt fine, but sometimes suffered from headaches and dizziness himself. He'd paid it little attention until today.

Now the shroud-wrapped figure was lifted out of the coffin and nestled directly in the earth, and the Hoca began a prayer. The others joined in, their voices tinged by pain and resignation. When they were finished, a worker began shoveling dirt into the grave. Perhaps the Hoca had a sudden vision of himself lying in there, facing upward, as if trying to catch a last glimpse of the sky before it was forever eclipsed. Then it would be his wife and his own children gathered around, praying and mourning.

After he was gone, death would then turn its sights on his children, and theirs. This was inevitable, but would their deaths also come too early? The thought pained him and would not leave his mind.

He murmured a few words to Mehmet's children, briefly clasping his cousins' hands. As he did, he noticed their fingers, and his own, and suddenly they saddened him. He knew them intimately, having lived with them his entire life, but a stranger might have noticed the small palms and unusually short, almost child-like digits. All of Kemal's siblings had such hands. Two of his daughters would have them as well, although the trait would not arise in one of his sons. All in all, about half his relatives had the feature.

This was the pattern: Slowly, too slowly, Kemal had realized that early death was selective in its victims, seeking out only those family members with short fingers.

He followed the mourners to the road, which was cloaked in blue shadows now that the fog had arrived and darkened the sky like an early dusk. As he closed the gate he took a last look back at the graves, now almost invisible through the filmy air, and thought once again of his children. At that moment he knew what he had to do.

Kemal's decision to search for help is the subject of a family legend and set off a chain of events that eventually brought me to this cemetery 48 years later, in the company of a group of scientists from Germany. We had come bumping up the road in a large, red van full to the brim with people and equipment. The vehicle was being driven by Kemal's son, Cafer, now in his mid-forties, who has stepped into his father's shoes as the community's religious leader. As he drove he chatted with his cousin Hüseyin, beside him in the front seat. Cafer pointed out the peaceful resting place as it jostled by. It now has a few more graves, including that of Kemal, who died of the same mysterious ailment as his uncle, and those of two of his brothers and a number of cousins who suffered the same fate.

Things have changed a bit in the intervening years. While the road is still rough and unpaved, the lush hills are now filled with hazelnut trees and carpeted with fields of tea in addition to maize, interrupted by the occasional house. The families now have cars and running water and electricity; some have televisions tuned to soccer matches, soap operas, or talk shows. Many even have high-speed Internet connections. These changes in lifestyle are a direct result of Kemal's search for help, because the doctor he eventually found suggested that the families grow tea and hazelnuts instead of corn. That had provided for only their most basic needs, with nothing left over to permit the purchase of cars or any other luxuries.

Within just a few decades, Kemal's son Cafer has personally witnessed the development of life in the village from medieval conditions into the 21st century. Elsewhere that transformation took centuries, and it gave cultures at least a bit of time to adapt. Here it has happened over four decades. As one of the first to have embraced computers and other features of modern life, Cafer has played a central role in the integration of sweeping changes into their lives. This huge responsibility has left him with the firm belief that education and progress are vital to the future of his family and his country. But in many fundamentally important respects, such as the quiet, peaceful practice of their religion and a lifestyle that depends on the farms, life goes on much the same as it has for a thousand years.

Cafer worked the gearshift constantly as he urged the van up steep inclines, around sharp corners, hugging the hill when there was a drop-off on the other side. It was good that the car was so full, he said. The weight gave the tires better traction. After a rain, or when the roads were full of snow, they became almost impassable.

I was surprised that it snowed here. Late October still felt like summer.

"Oh yes," Cafer said. "I'll show you pictures." Later he did: snapshots of his house, his car, the landscape hidden under a white layer that was a meter thick – more snow than we had seen in Germany for several years.

We were on our way to meet his extended family, who have become central players in a fascinating scientific story that began with the series of deaths in the family in the 1950s and 1960s. Their problem is unique. Except for a few relatives who have relocated to other parts of Turkey and Germany, they are among just a few people across the world whose genetic code is scrambled in a particular way, affecting a specific region of one of their chromosomes. But this causes a condition that may hold important clues toward understanding a much more se-

rious, worldwide health problem: a form of high blood pressure called *essential hypertension*. That hope has motivated Fred Luft's lab to pursue the story for the last two decades, in spite of considerable obstacles.

In the morning we had driven in on the wide new coastal highway, recently built by the Turkish government for a price tag in the billions. The project created a thoroughfare that starts near Turkey's eastern border with the Georgian Republic, runs westward to the city of Samsun, then drops inland toward Istanbul. Fifteen years ago this shore was cluttered with shops and apartment buildings and wharves crammed with fishing boats, all jammed up to the water's edge, so the only way to build such a road was to extend the coastline outward into the sea. Massive amounts of rock and concrete were used to create a wide new strip of land. Then years of work produced this rapid route connecting a long string of northern Turkish towns.

But the improvements stop directly at the shoulder of the highway; once you turn off, the roads dissolve into unpaved gravel. The way they fork and twist – with no names or signs – makes you wonder how anyone ever finds his way.

We had arrived the night before on a flight from Berlin through Istanbul to Trabzon and checked into a hotel near Samsun, a city of about 90,000 directly on the coast of the Black Sea. Before breakfast some of us had walked from the hotel down to the rocky beach. In October the water was as warm as the early morning air, and huge fishing boats painted in bright yellows and greens were preparing to sail out onto this vast sea that stretches to the horizon and beyond. If you turn away from the water and face the south, you are greeted with a panorama of low, tooth-like hills that march seemingly forever upwards and eventually become the foothills of the Samsun mountain chain.

This lovely, temperate zone offers a perfect climate for growing hazelnuts and black tea. Their harvest requires hard manual labor that provides a living for hundreds of thousands of farmers scattered in tiny communities like Cafer's. The region provides the majority of the world's hazelnuts. The people who live here are known for their warmth and an exceptional hospitality toward strangers. We were about to experience those characteristics in full force.

At a fork in the road Cafer wrested the car to a stop to pick up his son Ercan, a dark-haired eighteen-year-old with a backpack slung over his arm, on his way home after a week of boarding school in town. He tugged open the door and climbed in. He had known of our arrival but still stared at us in surprise: crammed into the van were his father and uncle, five researchers from Germany, plus a photographer and me squished into the seats. The back was piled full with large metal boxes containing medical equipment, two huge suitcases stuffed with medicine, and various bags that held laptops, documents and more equipment.

Mehmet slid a tiny folding bench from under the seat and handed it to his nephew, as if this were all routine, as if the car were often so overloaded that you needed extra seats. The boy perched himself on it near the door. It didn't look safe, but the car was so full there wasn't anywhere to fall, and he had as much room as the rest of us as we jostled up the road.

Around a curve, parked at a rude angle on the side of the road, appeared a battered blue jeep with rust spots. "Stop!" one of the scientists called. The doors of the van rolled open and everyone jumped out.

Maj Britt, a photographer and friend, shrugged at me; she didn't know what was going on either. "Reminds me of Chinese fire drills when I lived in New York," she said.

I had left the United States 25 years ago and couldn't remember what a Chinese fire drill was. I had never seen

people springing from a car at a red light in downtown Manhattan and racing around it. Nor had Ercan, who plainly thought we were all crazy.

Outside Sylvia Bähring, a tall blonde in her forties, passed her hand fondly over the jeep's hood. Sylvia has stood at the forefront of the research project for many years and now was making her fourth visit to the Black Sea. "This is the car," she said.

"That's it," Fred Luft agreed. It was a warm day and he shrugged out of his tweed jacket, hanging it over a shoulder. "We drove this thing around in 1994, the first time we came. It didn't look much better then. It's still running. Amazing."

The jeep was battered, pocked with rust and mud-splattered; the tires had almost no tread; parts of the body had been replaced but remained unpainted. This artifact brought home the fact that Fred and his colleagues had been coming here for 15 years. Now in his late sixties, with a dark head of hair steadily turning grey, Fred has devoted himself tirelessly to the project – alongside many other activities – and was ultimately responsible for our being here.

Most of the scientists had made the trip before; Okan Toka, a German doctor with Turkish parents, had even spent an entire year with the families. Each expedition has yielded new clues to the mystery of the family's health and raised new questions. Maj Britt and I had been invited along to make a record of the trip; it was our first time.

After a cigarette break we climbed back into the van and headed onward toward Cafer's house, a lovely yellow building that tops the summit of one of the hills. In front lies a large paved terrace, bordered by the house and a barn; the other side is open and provides a magnificent view of the sea and the jagged surroundings. From this vantage point I counted nine mosques tucked away in the nearby hills and valleys. Soon the muezzins would climb into the spires of the minarets, which rose from the landscape like ornate spears, and call the faithful to prayers in a quavering song. In modern times this is often done from the prayer hall, through a microphone and speaker system. It didn't matter; five times a day, their voices rise through the hills and merge in a magnificent harmony that surrounds you on all sides.

As I enjoyed the fresh air and Maj Britt snapped photos, the scientists unloaded their equipment and lugged it to the front door. At the threshold they kicked off their shoes, following the Islamic custom, to carry everything up to the first floor. Over the rest of the day they would unpack – transforming the small house into a makeshift hospital. In the living room they set up a table for interviews to collect information about family members and their health. Each person would be measured and photographed – with separate images of their hands and feet – in the dining room. The children's bunkbeds became a station for the blood pressure measurements, and the grandmother had to move out of her bedroom to provide a place to take blood samples.

Cafer beckoned me into his mother's room, where he climbed on the bed and lifted the corner of an embroidered cloth on the wall. It covered a black-and-white photograph of himself as a young child, nestled in his father's arm. This image, taken nearly 40 years ago, was my first glimpse of Kemal. In it Kemal was about Cafer's age, and there was a strong resemblance between the father and the way his son looks today. Later I asked Atakan Aydin, one of the two Turkish-speaking scientists along on the trip, why the image was covered. "Probably because his mother prays here," he said. "In the Muslim religion, it's not permitted to pray in front of a picture, statue, or photograph. You have to concentrate without any distractions."

This day was the culmination of six months of careful planning, of frustrating bureaucratic obstacles, and

Franz Volhard

dozens of phone calls to ensure that the family members would assemble to meet us. No – that wasn't right. The groundwork for our visit had been laid in the early 1960s. We were here as a direct result of the question that had been on Kemal's mind at a funeral, and of the brave steps that he took to try to answer it.

About 150 years ago, Cafer's great-great-grandfather married a woman from another town farther to the east. After six generations, her name has been forgotten and no one remembers precisely where she came from. What we do know is that she brought along an unusual bit of DNA that she passed along to some of her children, and they passed it along to about half of theirs. She may have inherited it from her own parents – meaning that somewhere to the east, there may be distant cousins with short fingers and high blood pressure. Or this disrupted bit of genetic code might have started with her, as unique mutation. Every human alive has such completely original "copying errors;" fortunately, most of them turn out to be harmless.

In this case, those who inherit the genetic information seem normal at birth, but their growth is a bit stunted and their fingers develop in a unique way. And with each passing year, their blood pressure rises. With very few exceptions, it reaches astronomical heights by middle age and those who are affected die, usually from strokes. The blood vessels in the brain can't handle the pressure.

By the time of our visit in October 2009, some of the reasons for the deaths had started to become clear thanks to long years of work on the part of Fred Luft's lab and a few collaborators working in other countries. Cafer's extended family has played an equally important role, allowing their lives to be turned on their heads in the name of science. Even nonaffected family members such as Cafer and his children have submitted to the discomfort of giving blood and tissue samples and stays in the hospital for extensive tests. They serve as an important control group: They share many of the genes of their relatives, except for that one troublesome bit.

The genetic condition that they have is unique; only a few families and individuals scattered across the globe have experienced something similar, through disruptions in the same approximate region of DNA. But Fred believes that the syndrome may hold the key to a much larger problem: the essential hypertension that directly leads to the death of nearly a quarter of the world's population.

I first met Fred three years ago in the much different context of his office. At the time he worked in the Franz-Volhard Clinic in the village of Berlin-Buch, a center for clinical and molecular cardiovascular research that belongs to the famous Charité University Hospital system. Fred has a second position at the Max Delbrück Center for Molecular Medicine, also in Berlin-Buch, where he has been a champion of attempts to translate what has been learned from molecular biology into the field of human health.

The clinic is named for a pioneer in cardiovascular research; I passed a portrait of Franz Volhard in the hallway. In it he is a young man with a violin tucked under his arm. Volhard combined research with a love of music, finding enough musicians among his staff to form a string quartet that entertained their colleagues and patients for many years. That appreciation for culture was still visible in the form of a grand piano that dominated the sunlit room where patients waited for their appointments.

During that first meeting I asked Fred why he had devoted so many years to a genetic problem that affected so few people. If you wanted to cure high blood pressure, wouldn't it make sense to concentrate on its more common forms?

"I get asked that all the time," he said. "The answer is pretty simple. We know that there is usually a genetic

component to major diseases – hypertension and cardiovascular disease, cancer, Alzheimer's disease, and so on. People who inherit particular forms of genes are more susceptible. But usually these conditions involve subtle interactions between many genes, and that makes them tremendously hard to find. It's much easier to pinpoint problems due to single molecules. Our hope is that the unusual cases caused by single genes will give us clues, point us to culprits that may be defective in the population as a whole."

A first hurdle may be identifying patients with those unusual genes – it might require a blood test and an expensive genetic screen. With this family the process is much simpler: short fingers and high blood pressure are always linked, so to find an affected person you need only look at his hands.

But the next step, actually identifying the gene involved, can also pose its problems. Painstaking work on the part of the lab over the years finally narrowed the search to a small region of a single human chromosome. That was helpful, but small is relative. Even this segment contained about 3.5 million bases of information.

Genes – the DNA sequences that encode proteins – are scattered along chromosomes, in tiny bits and pieces. Most genes are interrupted by long "non-coding" stretches that are edited out as the information is processed, ultimately to be used in making proteins. Although genes make up only a fraction of the total human DNA sequence, even a very small region might contain a lot of them. The segment initially identified by the group held about 102 genes.

But after many years of work to narrow this region down and identify the defective information, none of the genes seemed to have any direct defects. The molecules seemed to be "spelled" the same in affected and non-affected family members. This meant that the problem didn't seem to be a traditional mutation or variation, in which a letter or two of the code have become scrambled. Instead, it might involve one of the other functions of DNA that were being exposed by scientists, seemingly on a daily basis.

This has made the search that much more difficult, but also more suspenseful. As Fred says, "If we'd pinned the problem down to a mutation in a specific gene ten years ago, that probably would have spelled the end of the project, as far as we were concerned."

Instead, the researchers have had to dig deeper and deeper into the question of how information in the human genome builds a body. The team has used nearly every new type of biotechnology that has come along, applying it to cultures of cells taken from the human subjects and laboratory animals. So the attempt to answer a simple question has become a metaphor for the progress of biomedical research and the challenges that remain as scientists and doctors try to craft a new type of science at the intersection between biology and medicine.

2 A grandmother, a monk, and their gardens

One day in the early 1960s, Kemal asked a friend to take over his duties at the mosque. Like most of those living up in the hills, his family was poor and had no car, so he had to walk down the winding roads to the town on the coast, a trek that took a couple of hours. He arrived dusty and thirsty at the bottom and walked to the coastal road, where he waited for the bus to Samsun, another hour and a half away. At that time there was no smooth coastal highway; the bus followed the two-lane road that hugged the contour of the shore and passed through the center of every town, often impeded by mules bearing loads or trucks rattling toward the bazaars.

The distances and the lack of transportation meant that Kemal and his family only saw a doctor when faced with emergencies. It also put them far away from help when someone had a serious problem such as a stroke. Too often that is still the case, despite the construction of modern hospitals at intervals along the coastline. The situation may be changing, thanks to a new government program that could significantly improve medical care for such families. (We heard about the program during a nerve-wracking visit to the military police – a story for later.) But in the early 1960s, Kemal was not sure whom to see when he set out to find an answer to his family's health problems.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During the ride he stared out the window at the sea. A boy across the aisle said to his father, "That man is talking to himself." Kemal realized his lips had been moving. As a child, he had memorized the entire Qur'an, earning him the title of *Hafiz*, and learned to recite it in the proper slow and rhythmic way. There were different schools of recitation, and he smiled as he remembered heated arguments between his classmates over the rendering of some of the phrases. Often when he was occupied with a problem, verses ran through his mind and across his lips.

He had written the address of a doctor on a scrap of paper; when he stepped off the bus he consulted it again and asked for directions. He found the office in a narrow building between two shops on a cluttered street; the entry was almost hidden by wares from the vendors, which spilled out onto the sidewalks. Inside, Kemal approached a woman sitting at a desk and asked to see the doctor. When asked the nature of his problem, he didn't quite know what to say. He settled himself into the waiting room, briefly greeted a mother with a sniffling girl on her lap and an old man with a cane, and composed his thoughts.

After a while his name was called and he was led to an examination room. Here, too, there was a short wait, and he spent the time studying his surroundings and reflecting on the purpose of the strange collection of items to be found there. The functions of the scale were obvious, and those of the rubber gloves and syringes – farmers knew of the dangers of tetanus first-hand, and their children needed vaccinations before attending school. But many of the books on the shelves and the boxes of medications bore foreign names. Even the titles he could read meant nothing to him.

Finally the doctor appeared, greeted him, and extended his hand. Kemal shook it, thinking about his own hands, but the young man didn't notice anything unusual.

"What brings you here?"

By now Kemal had organized his thoughts and did his best to explain. Some members of his family had small hands – he extended them for an inspection – and many had died. There seemed to be a connection.

The doctor gently took his hands and turned them over, his curiosity aroused. He sat down on a chair, still holding them.

"Is everyone in your family like this?"

No, many were unaffected. But those with the problem had small hands and a small stature overall. Strangers often had a hard time guessing the age of the children and even the young adults. A girl in her mid-twenties was often mistaken for a teenager.

"And your wife?"

"No. She comes from another village. They don't have this."

The doctor leaned back in his chair. "Tell me about the deaths."

The brief descriptions Kemal gave were reminiscent of a stroke – a rupture of blood vessels in the brain – but it was impossible to be sure without more information. The Hoca had said enough, though, that the doctor thought he might be seeing a genetic condition. This was something they had learned about in medical school, and the doctor had seen cases such as color-blindness, deafness, and anemia that fit the classic patterns of hereditary syndromes. He had also learned that such conditions had no cures. The best you could do was treat the most dangerous symptoms. Unlike infections caused by bacteria or viruses, which could often be fought with antibiotics or vaccinations, modern medicine had nothing in its arsenal to address the underlying causes of genetic diseases.

The doctor reached for his blood pressure cuff and asked Kemal to raise his sleeve. He pumped on the bulb

until and lay the chestpiece of the stethoscope at the crook of the man's elbow. When the cuff was fully inflated, he began slowly releasing the air and listened for two telltale signs.

The cuff on Kemal's arm prevented blood from entering the brachial artery, which supplies the lower arm, until enough air had been released so that the pressure of the heart could overcome the restriction created by the sleeve. First the doctor listened for a loud thumping sound, which is the sound of the heart pushing blood through the artery. That gave him the first value – the *systolic* pressure, the point at which it reaches a maximum within the circulatory system. The gauge attached to the cuff showed him how much pressure the flow of blood was exerting on the arm, and this allowed him to read the value. Next he listened for a sharp drop in the thumping sound – as the pressure in the cuff dropped, it became almost inaudible. The value on the needle at that moment provided the second measure – *diastolic* pressure.

The systolic value represents the moment when pressure on the circulatory system is greatest – when the heart has just contracted and forced blood outward through the system. Between beats the heart muscle relaxes and the tension subsides just a bit, because the vessels are still full of blood. Evolution has enabled human vasculature to support a range of differences in this pressure without blood bursting through the vessels – which protects the system during times of stress or extreme physical activity. But below that range, organs may be starved of nutrients. Above it, the high pressure of the blood rushing through will stress vessels and other organs, putting a strain on them that they aren't equipped to handle over the long term.

Blood vessels in the brain are particularly susceptible when the system breaks down. The heart is usually affected as well – like any muscle, overwork can cause it to enlarge. An intriguing feature of the family's hearts became important later, after several affected members underwent a systematic medical examination.

In humans, a sustained systolic pressure of about 140 would be normal for an adult of Kemal's age. 160/100 would be considered dangerously hypertensive. And anything beyond that put you in the emergency room category.

Now he couldn't believe his eyes, and the readings almost made him fall out of his chair. Kemal's systolic blood value was 270 mm Hg. Diastolic 160 mm Hg. Kemal had a blood pressure of 270/160.

"Let's wait a minute and try again."The doctor's hands hands seemed to be shaking.

But a repetition brought the same results. Still stunned, he leaned back in his chair. It was a wonder the man was alive.

"Do you get headaches?" he asked.

"Yes."

"Do you get dizzy?"

"Occasionally."

In any other situation he would have called an ambulance and rushed the patient to the hospital. And normally he would have regarded Kemal as a unique case, but if the family turned out to have a history of deadly strokes, the problem might be much more widespread among them.

At that point the physician had reached the limits of his competence. "I would like to help, but there is really nothing I can do," he said. "I would strongly advise you to visit the hospital in Ankara, and do it as soon as possible. They may have a specialist who can tell you more. If you go, you might take someone else from the family along, someone who also has such hands. It's best to look at more than one patient."

The city was far away, halfway across the country, a much longer ride by bus. For a moment the thought of such a long journey depressed him, then Kemal was ashamed of himself. *Did you expect a miracle – that he would give you a pill and this would all go away?* All right then, he would go to Ankara. He could take his younger brother Ali, and they could stay with a cousin who lived there.

"Would you like me to examine you while you're here?" the doctor asked.

What use would that be? the Hoca thought. He thanked the doctor and made his way to the door.

We live in an age in which headlines report the discovery of new connections between genes and disease nearly every day. Particularly since the 1960s, a wide range of hereditary diseases have been discovered and new methods have been developed to diagnose them. As far as real treatments go, for most physicians the basic situation faced by Kemal's doctor has not significantly changed. "You do your best to alleviate the symptoms," Fred Luft says, "all the while knowing that you're not addressing the problem at its source."

With the exception of a few tentative, experimental clinical studies, there are no cures for genetic diseases. Unlike infectious diseases, where the enemy is usually an invading bacteria or virus, hereditary conditions spring from information harbored in every cell in a person's body. It can't be removed or destroyed.

On the other hand, a century of research has shown scientists where to look for the information in cells, what molecule it is made of, and often some of the details of the changes that genes undergo to produce a disease. But this knowledge has come only very recently, and it has been hard-won.

Heredity is a mystery that has intrigued people since before the beginning of recorded history. Ancient farmers noticed that the offspring of plants and animals usually resembled their parents more closely than distant relatives. They made practical use of this observation to select and breed crops and livestock with desirable qualities. In the new generations, those characteristics were usually more frequent, often more pronounced. These practices have been responsible for creating virtually all the food and domestic animals that we know today.

Most of the natural ancestors of these species were so different in prehistory that if you could travel back in time, you'd have a hard time finding something to eat. The maize that Cafer and his neighbors raise to feed their animals is a good example. The tall stalks have their origin in a tiny plant called *teosinte*, native to Central America. Cultivation over thousands of years produced its modern forms. In modern times, researchers have discovered that this process involved changes in a mere five genes. Cabbage, broccoli, Brussels sprouts, cauliflower, and kohlrabi are descendants of a single common ancestor that was cultivated in different ways, emphasizing various parts of the plant. Broccoli was chosen for its stems and flowers; kohlrabi developed as farmers turned their attention to a part of the plant called the storage stem, and cauliflower is the result of selecting luscious flower clusters. Hybridization – the crossing of different species – has also been essential to the production of modern food. Wheat arose from a combination of wild *einkorn* with goat grasses. In the process, the species has acquired about three times as much DNA as a human.

Domestic animals have gone through a similar process. Every dog alive today descends from a wild, wolf-like ancestor that lived at least 15,000 years ago. The amazing variety that can be seen in modern pets arose through selection and breeding: tiny Pekingese, for example, were bred by the Chinese for their resemblance to the spirit

lion of Buddha. Other varieties were selected for practical reasons, such as their hunting abilities.

Sometimes these changes come with a price: breeding closely-related animals over many generations may lead to an accumulation of unusual forms of genes that may be harmless if an animal only inherits one copy, deadly if it inherits two. Such pairings-up are much more likely unless fresh genes are brought in from time to time by mating animals that have more variety. A similar phenomenon can be found in human populations: many of the hereditary monarchies of Europe, for example, exhibit genetic conditions that come from centuries of marriages between close cousins or other near relatives. While pursuing a mystical program of "preserving the blood line," many of these families have developed hemophilia and other genetic diseases. This may have been most pronounced among the rulers of ancient Egypt, where pharaohs frequently married sisters or half-sisters. Their mummies often reveal signs of debilitating genetic diseases.

A similar case is recorded in a book by the well-known neurologist Oliver Sacks. In *The Island of the Color-Blind* he recounts a trip he took to the a tiny island among the atolls of Micronesia. Many of the inhabitants of Pingelap suffer from a hereditary condition called *complete achromatopsia*. This genetic disease is the result of a mutation that leaves people totally color-blind. The defect makes them unable to construct color information out of the information received by their eyes.

In normal human populations this condition usually occurs only once among every 33,000 births, but on Pingelap nearly five percent of the population has inherited the full-fledged condition. And about 30 percent of the population probably carries a recessive mutation that can cause it to reappear in future generations.

Tradition ascribes the cause to a tidal wave that swept over the low atoll around the year 1775. The wave killed everyone except for 20 members of the royal family – at least one of whom suffered from the disease, and many others were likely carriers. The isolation of the island meant that strangers rarely arrived to mate with the locals, so the trait has become firmly established in the population's gene pool.

Even without inbreeding, troublesome characteristics can be passed from parents to children, and Jewish tradition offers tantalizing evidence that people recognized this long ago. The circumcision of baby boys is required by ancient law, but an exception was made for families known to suffer from the blood disease *hemophilia*. People with this condition lack a molecule that helps blood to clot, which means that an injury or the cut made during circumcision can lead to fatal, uncontrollable bleeding. Rabbis ruled that if a baby's uncle on the mother's side had died this way, the ceremony did not have to be performed. After long experience and many deaths, they had recognized that hemophilia was a hereditary disease and that it had something to do with the mother's side of the family. Today we know the reason: the clotting factor is encoded in a gene that lies on the X chromosome, which men always inherit from their mothers.

But such intuitive insights into genetic principles remained few and far between until about 150 years ago. The true extent of people's ignorance about heredity is evident in a story from the early eighteenth century, when a young English woman named Mary Toft generated a flurry of excitement among some of the leading scientists of the day. The case is interesting not only for what it reveals about scientific knowledge of the time, but also because of the woman's brief, spectacular flirtation with the media. Today there are a lot of Marys: people who do outrageous things to thrust themselves into the public spotlight, hoping to capture a moment of fame. In her day she couldn't spin her story into reality shows or YouTube videos, but newspapers were happy to give her headlines, and the result was about the same.

On November 9, 1726, the doctor and midwife John Howard arrived at Mary's home to deliver a baby that was about a month overdue. He was about to receive the shock of his life: Emerging from Mary's birth canal was a "creature resembling a rabbit, but whose heart and lungs grew without its belly." The story in *Mist's Weekly Journal* goes on this way:

> *"About 14 days since she was delivered by the same person of a perfect rabbit; and, in a few days after, of 4 more; and on Friday, Saturday, and Sunday, the 4th, 5th, and 6th instant, of one in each day; in all nine. They died all in bringing into the world. The woman hath made oath, That two months ago, being working in a field with other women, they put up a rabbit; who running from them, they pursued it, but to no purpose: This created in her such a longing to it, that she (being with child) was taken ill, and miscarried; and, from that time, she hath not been able to avoid thinking of rabbits."*

At the time it was commonly believed that experiences during pregnancy could influence the characteristics of an unborn child, but for a woman to give birth to rabbits was a stretch for even the most credulous readers. The King ordered an investigation in which Mary Toft and her doctor were brought to London. On December 1 she seemed to be going into labor again; it didn't stop her from enjoying a large dinner including, ironically, a dish of rabbit. "Great numbers of the Nobility have been to see her," reported the London Journal, "and many Physicians have attended her, in order to make a strict Search into the Affair; another Birth being soon expected."

The hoax was finally exposed when a prison attendant admitted that Mary had asked him to buy a rabbit at the market. A judge threatened to subject her to an "extremely painful procedure" if she refused to tell the truth. Finally she confessed to having made up the whole thing with the help of a partner who inserted the animals into her birth canal. Although she was put on trial for fraud, she was released without punishment, perhaps out of pity for a woman so desperate for a moment of fame.

Over the next century, a few scientists made serious attempts to understand how parents pass traits to their offspring. Twenty-five years after newspapers covered Mary Toft's story, the French doctor Pierre-Louis Maupertius tracked the appearance of extra fingers through four generations of a family and constructed family trees of albinos – people who lacked pigment in their skin and eyes. Half a century later, a British physician named Joseph Adams recognized that mating between close relatives frequently led to disorders. He also noted that some of these diseases only appeared late in a person's life, and that the environment often affected the way they developed.

But it would take many more decades before the study of heredity became a true science, and it came about in a way that would seem unlikely today. The founder of modern genetics was the son of farmers, a failed teacher who became a monk, and he made his discoveries in a Catholic monastery.

During our visits to Cafer's house on the Black Sea in 2009, his mother Gül – the widow of Kemal – was a constant presence. She could nearly always be found outside, bearing a stick to herd the family's two cows down a steep path, or sitting on a corner of the terrace shelling beans. Her head was always covered with a brightly patterned scarf, but it didn't hide eyes the color of a blue sky and sharp features that are echoed in the faces of her son and one of her granddaughters.

She chattered as she worked. I couldn't understand a word she said but admired the calm way she went about her business: first whacking a lumpy burlap sack with a stick, then emptying it on a blanket to peel broken husks off the beans.

The pods were whitish-brown, about ten centimeters long. She nimbly peeled them open to reveal the seeds: some brown, some a milky white color, and others a mottled mixture of the two. Atakan, one of the Turkish-speaking researchers, asked her, "Have you ever wondered why one plant makes beans of different colors?"

Her hands paused a moment and she inspected him with those clear blue eyes. Then a shrug. "It's God's will," she said.

It was a phrase we would hear again, a few days later, at the home of her brother-in-law Ali. At 62, he is the oldest living member of the family to be affected by Bilginturan's syndrome. "It's God's will," he said, referring to his hands and his high blood pressure. This clearly wasn't a stance against science; it was fine by Ali if God wanted to carry out his will through the activity of genes.

An early death might also be God's will, Fred Luft would probably say, but your wife and kids probably won't like it. And finding a way to prevent it must be God's will, as well.

While taking blood samples and putting the family through other procedures, the scientists have done their best to explain that these health problems can be attributed to information contained in their DNA. Even so, the attitude of Gül and Ali is typical – and perhaps it's a larger lesson: One should accept what cannot be changed. Maybe this is the healthiest mental approach to coping with the unique genetic legacy passed along by their parents, which has led to a condition that cannot yet be cured.

Atakan's query about the beans has a deeper significance, however. A century and a half ago, the same basic question gave birth to the modern science of genetics. So ultimately, whatever we understand about the family's disease today started right with those beans.

All right, the early work involved peas, but beans would have served just as well.

Gregor Mendel was born in 1822 to a family of hard-working farmers probably much like Cafer's. They had land in Moravia, a region that now lies within the borders of the Czech Republic. The few photographs that exist give us a glimpse only of Mendel as an adult: a square-faced man with a heavy jaw, a receding hairline, a blunt nose on which small round eyeglasses are perched, and he's just about to frown – maybe thinking about the administrative battles that have occupied his later years. The clergyman is evident; he has a sort of placid agelessness, but the prankster is there, too. Mendel had a reputation for practical jokes that sometimes didn't come off too well. To me he doesn't look troubled, or bear the signs of having survived an exhausting series of personal setbacks.

Frail and often sick as a child, he was unsuitable for a life on the farm; academically, a series of almost pathological attacks of nerves before tests made him perform poorly even in his favorite subjects – physics and mathematics.

He finally found refuge in an abbey, which served a vital social function as a center of wider learning as well as religious training and was a common destination for young men interested in science. The life of a pastor or priest offered leisure time for breeding plants or collecting beetles. Twenty years earlier another "failed" student – Charles Darwin – had pursued the same option. He was studying to becoming a country pastor in England, not very successfully, when he got the chance to join a cartographic expedition that would sail around the globe. The ultimate result was to turn him into one of history's greatest scientists, who produced a theory of life that changed the world.

Mendel was taken in by St. Thomas in the town of Brnø, run by a liberal and relaxed order of Catholicism called the Augustinians. Today the basilica and its monastery lie in the middle of a modern town, surrounded by high-rise apartment buildings that didn't exist during Mendel's day. But the wings of the abbey still encompass a peaceful grassy space that served as a garden. In the late 19th century its centerpiece was a modern greenhouse that was built specifically for Mendel's experiments. Although the structure has disappeared, the stone foundations have been preserved as a memorial to the father of genetics.

He entered St. Thomas in 1843 as a novice, changing his name from Johann to Gregor. He was rushed through his training because many of the priests had caught infections and died after tending to sick parishioners at a nearby hospital. So at the earliest possible age, 25, Mendel was ordained and thrust into a working life of dealing with the sick and needy. The stress sent him to bed for weeks with another nervous attack that might have triggered a complete breakdown had it not been for the help of St. Thomas' abbot, a progressive, sympathetic man named Cyrill Napp. Here Mendel found a kindred spirit: Napp was an avid amateur scientist who carried out breeding experiments on sheep as a hobby and encouraged the young monk to pursue his own scientific investigations. Napp took extraordinary measures to support him, for example, by building a state-of-the-art greenhouse.

In Brnø Mendel began working on heredity, first in his own room. He crossed albino mice with wild rodents in hopes of detecting hereditary patterns. This would bring another setback during an inspection of the abbey by a visiting bishop. He was shocked to find animals mating in a monk's room, so the mice had to go.

What looked like another piece of bad luck actually turned out to be a blessing. Animal heredity is extraordinarily complex, which means that the experiments probably never would have produced clear results. Fortunately, Napp had already given Mendel a plot in the abbey's experimental garden, where he could breed plants. No one objected to that because, as Mendel noted ironically, "The bishop did not understand that plants also have sex."

Gregor Mendel

In 1856 he took the train to Vienna to take examinations in hopes of earning a teaching certificate; once again, an attack of nerves led to another failure. There is an apocryphal story that he got into an argument with the head of the Botanical Gardens in Vienna, who disagreed with some of his "modern" scientific views – including a statement that male and female parents contributed equally to the characteristics of their offspring during the process of heredity. Though a number of scientists were coming to believe this, many disagreed, and Men-

del discovered that a single conservative professor on the examination board could derail a student's career.

So it was back to the abbey, where he was allowed to teach without a certificate, and the students praised his courses. Finally there were no farm chores, exams, or parishioners' problems to attend to. He now had the freedom to tackle his favorite subject in a rigorous scientific way in the new greenhouse. Over the next few years he worked with numerous plants but, like many of his contemporaries, was particularly interested in peas. The way they reproduced – and the fact that they had lots of seeds – made them ideal for genetic studies.

Fertilization in most plants happens when pollen from the male sex organ, the *anther*, moves to the *stigma* of a female. A plant may pollinate itself, or there may be a transfer from one to another by bees, moths, or other insects. In peas the male and female organs lie within an inner compartment of the flower called the *keel*, and the entire process takes place there. So under normal circumstances in the wild, a pea plant mates with itself, serving as both father and mother in generating fertilized eggs that grow into new seeds.

There was, however, a method to raise peas from different parents. Mendel carefully cut open the keel of one plant and removed the anthers with a pair of tweezers. He collected their yellowish pollen on a brush and moved on to the next plant, the "mother," opening its keel to brush the pollen onto its stamen. He had already removed the anthers of this plant to ensure that it did not pollinate itself. He closed the keel again and wrapped it in a small bag so that it could not be reached by free-floating pollen or flying insects.

Mendel's approach allowed him to succeed in discovering the basic principles of heredity where many other scientists, including Charles Darwin, had failed. First, rather than trying to understand a plant as a whole, a muddled mixture of all kinds of characteristics, he focused on single features like shape or color. He started with the hypothesis that each trait acted as an independent unit. A seed's color, for example, might be passed down from parents separately from its shape or size. There was no real reason to make this assumption except that it simplified the experiments, but it turned out to be a brilliant idea. Everything Mendel went on to discover stems from it.

Another factor in his success was the precise way he carried out his experiments, eliminating every conceivable source of contamination and making an exact accounting of the results. His background in statistics gave him the skills to make sense of patterns in the numbers, and it also makes him the first person to have rigorously applied mathematics to a biological question. (Today these fields have come together in computational models of living systems, one of the fastest-moving areas of biology.)

Finally, Mendel avoided a mistake made by many others: Rather than expecting to see all the rules of heredity at work in a single generation, he followed the fates of plants for many rounds of reproduction.

He chose seven features of peas that could be clearly identified and tracked. For example, one strain of plant produced smooth, round peas. Another strain appeared identical except that its seeds were wrinkled. When Mendel first received seeds of the plants through the mail, he discovered that round-pea parents occasionally produced wrinkled offspring. For two years he bred the plants repeatedly until they always gave the same results. This process was necessary for all the traits he wanted to study, including the color of the seeds (yellow or green), and whether the plants had purple or white flowers.

Once the strains were stable, Mendel began crossing them. He opened the keels of plants that produced round peas and fertilized them with pollen from the wrinkled-pea strain. In another corner of the greenhouse

he reversed the sexes and did the same thing, introducing round-pea pollen into wrinkled-pea plants. Intriguingly, either way, all the offspring were round. Rather than drawing any conclusions from this, Mendel waited a year, planted the first generation (called "F1") seeds, and now allowed the plants to fertilize themselves the natural way, which would mix up whatever hereditary material they had inherited. The F1 plants produced 7,324 second- generation peas (F2), of which 5,474 were round and 1,850 were wrinkled. This was almost a perfect three-to-one ratio, and other plants yielded almost identical results for the other features. Mating yellow- and green-pea plants produced only yellow seeds in the first generation, but about a fourth of the next one was green.

Mendel's brilliant explanation of this behavior forms the starting point for modern genetics. He realized that each of the features he was studying (for example, wrinkled versus roundness) was composed of two "elements" – one inherited from each parent. One was *dominant* and the other type was *recessive*, meaning that if a plant inherited one element of each type, the peas would take on the dominant form. This explained why the first-generation peas were all round: Each had inherited a round element from one parent and a wrinkled from the second. It made no difference which parent had contributed which element – the results turned out the same. Mendel had proven that the two sexes contributed equally to the characteristics of the offspring, a point that had caused him to flunk his university examinations.

The vocabulary of modern genetics didn't yet exist, but 40 years later other scientists invented names for Mendel's concepts. His "elements" became known as *genes*. The gene that determines a pea's shape naturally occurs in different types – one for roundness and another that wrinkles them – which we now call *alleles*.

The principle of dominance also explained what happened to the second generation of peas, when the F1 plants fertilized themselves. Now each of the parents had one dominant and one recessive allele, and their seeds received a random combination of the two traits. Chance dictated that about one fourth of the offspring received two round elements (producing round peas); another fourth inherited two recessive, wrinkled elements (making them wrinkled), and two-fourths received one of each, again giving them the dominant form (roundness). These patterns would continue in all future generations bred from peas from the F2 plants. The other traits that Mendel studied behaved in the same way. This meant that the color of peas and flowers were likewise determined by genes with dominant and recessive forms.

When he mated these plants, all the seeds in the first generation were yellow and round, as anticipated. He anxiously waited to see what would happen with the second generation. More experiments confirmed that color, shape, and other traits were produced by separate genes passed along independently from the parents.

In 1865, after 11 years of examining tens of thousands of plants and counting hundreds of thousands of peas, Mendel mounted the podium in the hall of the town high school to present his results in two lectures to a local scientific society. By this time he had extended the work to other plants, including beans, and obtained the same results.

The society's members included university researchers, teachers, and amateur science-lovers. About 40 people were present at his first lecture. The audience appeared interested, but they were clearly unable to judge the importance of what they were hearing. The publication of his paper "Experiments on Plant Hybridization," in the *Proceedings of the Brno Scientific Society*, received about the same response. Although the journal was sent to at least 120 European libraries, scientists did not understand that the article represented the first real scientific insights into the ancient mystery of heredity. There

is an apocryphal tale that even Charles Darwin received a copy, which was later found in his library. Supposedly its pages were uncut, which meant that it hadn't been read. (The pages of books and journals were printed in such a way that pages were left folded at the edges; to read them, you had to separate them with a knife or letter-opener.)

Mendel personally sent the article to Carl von Nägeli, a Swiss professor working at the University of Munich. It was important to have his results verified, and the famous professor might be the right person to do so. Mendel had already been working with a plant called hawkweed, which Nägeli had dabbled with, and mentioned this in the letter.

If Mendel thought his string of bad luck was finally about to come to an end, he was about to receive another devastating blow. Nägeli was pursuing his own hypothesis: that organisms inherit a bit of information from each parent and then blend it into an intermediate form. He responded that the results were interesting but insufficient to justify an entirely new theory of heredity. Mendel humbly offered to assist the professor without pay. Nägeli sent hawkweed seeds of his own and encouraged Mendel to raise them.

This plant turned out to be the worst possible starting point for genetic studies. The stamens of hawkweed are so tiny and close to the pistil that they can only be separated through painstaking work under the microscope. Even when Mendel managed, the experiments failed because of an unusual property of the plant.

In some cases, hawkweed reproduces *parthenogenically* – a type of cloning in which only the genes of the mother are used to create offspring. There was no way to know this, but it threw off the results and caused Mendel to begin to doubt his own conclusions. In 1869 he once again addressed the Brnø Scientific Society, to report on the work with hawkweed and retract his previous hypotheses. It was a setback both for the man and for science as a whole. This was particularly tragic because Mendel's work not only provided a completely new pathway for studying heredity; it also represented the first real application of statistics to a biological problem, an approach that has become central to modern biology.

Soon afterwards, Mendel was elected abbot of the monastery. He spent the last 20 years of his life immersed in administrative tasks and taking part in city committees. All this left little time for research, although he continued some work with bees and plants. After his death the next abbot burned his collection of papers, probably to get rid of sensitive documents related to abbey politics. In the process, he likely destroyed notebooks and other records that might have told us more about Mendel's scientific work. The many historians who have visited the abbey in search of traces of his life have left almost empty-handed.

It would take three decades for other researchers, working much the way Mendel had, to realize the importance of his work and make his name famous throughout the world. Too late to do him any good – by that time, Mendel had been dead for 16 years.

Today Mendel's experiments are recounted in school textbooks across the world, including those used by Cafer's children. The story may mean more to them than their classmates: Right at home they have a visible example of the principles the monk discovered, as close as their own hands, and the pressure created as blood runs through their vessels. Unlike the smoothness of a pea and its color, these two features are inherited together. If a person has one, they have the other. This doesn't con-

tradict the principle that genes themselves are inherited independently, for reasons that will come up later.

The first doctor that Kemal visited surely suspected that he was looking at a genetic disease, but proving it was a different matter. Unlike peas, people don't produce a new crop every year, and researchers don't have hundreds of thousands of subjects to work with. Nor can a scientist choose who mates with whom according to a strict experimental plan.

Proof that Kemal and his family suffered from a genetic disease would require a careful scientific study, the only way to establish a connection between short fingers and sudden death among his relatives. In the 1960s there weren't many people who could have carried out such a study. Finding the right person would take several trips to hospitals in other cities and ultimately Ankara.

During one of those trips, Kemal had the great luck to encounter someone who could help. Had that meeting not taken place, this book would not have been written, and his family would probably be no wiser about their state of health. And many who have survived would very likely not have done so.

3 A short history of short fingers

In December 2009 we followed Kemal's trail to Ankara. From the air, Turkey's capital sprawls across the high continental inland as a vast labyrinth of twisted streets, parks, and modern high-rises, settled into a plain ringed by high brown mountains. Lording over the city is an ancient citadel crafted from the same grey stone as the bluffs it stands on, with foundations lain in the third century B.C.E. To get there you climb through narrow, crooked roads lined by tourist shops, and at the top you are rewarded by a panorama of contrasts: tall new office and apartment buildings in bright colors, and an endless spread of houses with red tile roofs that follow the dips and rises of the town's geography. One side faces another steep, rocky bluff containing a patchwork of thousands of tiny houses that seem to spill down the slope.

The citadel overlooks a rugged landscape that has been settled since prehistory. This part of the world spawned one of the earliest advanced civilizations, and ever since people have fought over it. The region has been occupied by the Hittites, Phrygians, Persians, Greeks, Galatians, Romans, Byzantines, Turks, and others. All have left their traces in the form of artifacts, architecture, and artistic masterpieces. Constantly these products are turned up by farmers digging in their fields.

Many of these pieces are housed in the Museum of Anatolian Civilizations, located on the south side of the citadel in low, domed buildings built in the 15th century as a market and travelers' inn. It's a beautiful museum, with a central room that houses monumental reliefs, such as a series of waist-high friezes depicting the Epic of Gilgamesh, along with carvings of sphinx-like figures, chariots bearing archers, and musicians. The outer rooms carry visitors along a time-line of the region's history. The oldest artifacts are among the loveliest, such as the figure of a Mother Goddess rendered in ruddy clay, seated between two lions. Her thick body is reminiscent of the "Venus" figures found in Austria, France and Germany – remnants of much earlier Paleolithic cultures. Drawings and depictions of the Goddess are found throughout the region, including massive figures carved into mountainsides.

In a nearby case stands a gleaming bronze stag with tall antlers and a body decorated with whorls and patterns, found in a Hittite grave dating back over 4,000 years. One of the most exquisite figures represents a slim female figure made of an alloy of silver and bronze, ornamented with a thin strap that crosses her torso, her wrists and ankles decorated with metal rings. Nearby, a bronze mother presses a baby to her breast. In place of eyes are gaping holes that give her an owl-like appearance.

A piece that is not here – but would fit in well – is the "Dying Gaul," one of the most famous sculptures of classical antiquity. The story behind it is intimately bound to this region. The work was commissioned by King Attalus of Pergamon, a great kingdom to the west that spanned about half of present-day Turkey, to celebrate his victory over the Galatians. It depicts a soldier wounded in a battle near Ankara and pays tribute to the heroics of the defeated warriors. The original sculpture disappeared long ago, but it has been reproduced many times throughout history. The oldest and most beautiful copy, crafted by the Romans, resides in Italy and has a power which can't be captured in words. That didn't stop the English poet Lord Byron, who saw it during his adventuresome youth, from giving it a try:

He leans upon his hand—his manly brow
Consents to death, but conquers agony,
And his drooped head sinks gradually low—
And through his side the last drops, ebbing slow
From the red gash, fall heavy, one by one…

But the best impression of Ankara's rich recipe comes from a walk through the city streets. Below the castle lie the ruins of Greek and Roman temples, tucked between later structures, and an impressive amphitheater. Modern times have likewise seen the construction of some amazing architecture, such as the high-pillared tomb of Cemal Kemal Atatürk, who ushered the modern Turkish republic through sweeping cultural reforms such as a strict separation of religion and state.

The Kocatepe mosque, one of the largest in the world, was being planned right around the time Kemal first arrived in the city and its elegant minarets can be seen for miles. We didn't have time for a visit during our short stay, but Kemal probably couldn't have resisted during one of his later trips.

At the foot of the citadel lay the new university hospital, a sprawling complex of buildings that lies between the ancient and the modern. It had been constructed three years earlier and established with the opening of a Children's hospital; schools of nursing and other departments had just moved in. It was already becoming one of the most important medical centers in Turkey. Today it serves the four million inhabitants of the city and many more from the surrounding regions.

Hospitals in the 1960s didn't have departments devoted to human genetics. "At that time the topic

was lumped together with pediatrics," says Sylvia Bähring. With Hacettepe hospital's emphasis on children's medicine, it was probably the best place to go find someone curious enough and with the right skills to help Kemal's family.

At the hospital he eventually found his way to a physician named Mehmet Sonel. I haven't been able to discover much about Sonel, except for a curious coincidence: Earlier papers showed he had already been thinking about the genetics of short fingers, for a completely different reason. This colored the way he thought about the case and may have prevented him from taking things farther.

Sonel had recently come across a few people suffering from a very rare defect involving hormones. His patients' condition had the unwieldy name *pseudohypoparathyroidism*. Like most scientific tongue-twisters, it's a term made for precision rather than simplicity, and doctors commonly abbreviate it as PHP.

Fred Luft dissected the word for me. "*Parathyroid* refers to small glands in the neck that produce parathyroid hormone," he says. "That molecule isn't as well-known as insulin or estrogen or other hormones, but it has some important jobs in the body. For instance, it controls the amount of calcium in a person's blood – which in turn is crucial for all kinds of things. *Hypo* means 'too little,' so if a person's body doesn't produce enough of the hormone, we call their condition hypoparathyroidism."

The rest of the word – the prefix *pseudo* – comes from the fact that different problems sometimes cause similar symptoms. Fred compares the situation to a silent cell phone. "Your phone may not ring simply because your friends are busy and the telemarketers haven't got your number yet," he says. "Or you might not hear it because the battery on the phone is dead. In the first instance, the problem lies with a missing signal; the latter case involves a defect in the receiver mechanism. Pseudohypoparathyroidism is like the second case. The body produces parathyroid hormone, but cells are unable to take the 'call'. So the receptor can't transmit the message farther, and the cell doesn't get the message."

A parallel situation occurs with other hormones, such as insulin, and this explains the difference between type-1 and type-2 diabetes mellitus. In the first type, the body has lost the cells that normally manufacture insulin. If on the other hand, the hormone is present and cells stop responding to it, a person develops type 2.

"A frightening number of people have developed type-2 diabetes," Fred says. "In modern industrial societies, this disease has reached epidemic proportions. Genetics may partly be responsible, but most of the problem has to do with diet and behavior. As a doctor the first thing you do with these patients is get them to exercise and eat reasonably. Oftentimes that's enough to control the condition."

Problems related to hormones sometimes cause changes in the way the body forms. People who inherit PHP, for example, are typically shorter than average. And they usually have very short third and fourth fingers on their hands, because the bones called *metacarpals* that connect these two fingers to the wrist never reach their normal length.

Sonel recognized that Kemal's hands didn't match the typical pseudohypoparathyroidism pattern – all of his fingers were short, not just the outer fourth finger. In-and-of itself, that didn't mean much. Building bones, bodies, and fingers requires the participation of many genes. Individuals may have slight variations in other genes that change how another problem manifests itself.

Another thing that distinguished the case from PHP was Kemal's extremely high blood pressure, which wasn't one of the symptoms. The presence of hypertension was rather nonspecific. He might have PHP in combination with other problems; after all, hypertension is very common. But when Sonel probed the family history he discovered that there was probably a connection. Early

death seemed to have struck only those with short fingers. Something else was going on.

It left him with a puzzle he couldn't solve. He hadn't heard of other cases like this, and couldn't find any in his medical journals. The only thing he could do was to mention Kemal in an article about his other patients with pseudohypoparathyroidism and hope it would make sense to someone else.

Fingers have interested researchers since the earliest days of genetic science. When the 18th-century mathematician and philosopher Pierre Louis Maupertius discovered a French family with extra digits, he drew a genealogical tree to chart their occurrence, but he was unable to detect a pattern.

A true genetic study of human beings had to wait another 150 years, for the rediscovery of Mendel's work at the beginning of the 20th century. That happened thanks to three researchers working independently in in Europe: Hugo De Vries in Holland, Carl Correns in Germany, and the Austrian Erich Tschermak von Seysenneg. None of them knew of the monk's work when they started, they claimed. But each used a methodology similar to Mendel's and came to similar conclusions, although Tschermak's interpretation was full of mistakes.

De Vries was a Dutchman whose passion for science began in high school, where he won awards for science projects with plants. He began his university studies in the city of Leiden, where he immersed himself in Darwin's theory of evolution, then did graduate work in Heidelberg and Würzburg, Germany. Later he moved to Amsterdam, where he was offered a professorship at the newly established university and was appointed director of the Amsterdam Botanical Institute and Garden. In the late 1880s he began considering the problem of heredity and tried to integrate new concepts from his studies of plants with evolutionary theory. In particular, he proposed that traits were encoded in "particles" which he called *pangenes*. Twenty years later the Danish botanist Wilhelm Johannsen shortened the word to "genes", thus giving a name to one of the central concepts of modern biology.

By the turn of the century, de Vries was studying a huge number of plants and demonstrated that the principles discovered by Mendel held true in 20 different species. He hadn't been aware of Mendel's work – he had been on the verge of publishing his own work when a colleague sent him a copy of the monk's original article on peas. Learning that his findings weren't new must have come as a shock, but when he sent off his paper entitled "Concerning the Law of Segregation of Hybrids," he acknowledged Mendel's findings. The article was published in 1900 in the journal of the French Academy of Sciences.

Ironically, the second "rediscoverer", Carl Correns, had been encouraged to become a botanist by Carl Nägeli – the professor who had discouraged Mendel. Carrying out experiments with corn, Correns found the same type of rule-governed behavior that Mendel had observed and came to many of the same conclusions. He published his findings in an article called "G. Mendel's Law Concerning the Behavior of the Progeny of Racial Hybrids," which appeared two months before De Vries' work.

Erich Tschermak also had a biographical connection to Mendel – his grandfather had been one of the monk's professors at the University of Vienna. When the young scientist read of experiments carried out on peas by Charles Darwin, he began repeating Mendel's work, again without realizing it. He summarized his results in his university dissertation, which was reprinted in the Austrian journal of experimental agriculture.

In general, the three publications showed that Mendel's principles held true in a wide range of plants be-

yond peas. Even so, widespread recognition for Mendel's accomplishments eventually depended on one of the first great "popularizers" of modern science: the biologist William Bateson, who was carrying out his own breeding experiments in England. While riding on a train to give a lecture in London, Bateson read De Vries' paper with its reference to Mendel; he immediately realized that the laws could lay the groundwork for an entirely new science of heredity. He began inventing terms and concepts for the field.

Bateson became a passionate advocate for the infant field – even naming one of his sons "Gregory" as a tribute to his new hero. He had Mendel's original paper translated into English so that it would be widely read. In 1902 there followed a book called *Mendel's Principles of Heredity: a Defence*; Bateson made sure that scientists across the globe got a copy. This time people paid attention.

"Bateson would have enjoyed our story," Fred says. "He admonished his disciples to 'Treasure your exceptions.' From these strange cases, so much can be learned – and the patients in this family are certainly exceptions, as well as being exceptional."

The sudden flood of evidence for Mendel's ideas revolutionized the way researchers thought about heredity. Within a decade, scientists were investigating the laws in an even wider range of plants and animals and had begun to put them to practical use. In the United States, for example, large agricultural stations were set up to create better crops such as corn, beans, wheat, and tobacco based on genetic principles. This was a systematic approach to what farmers had been doing intuitively for millennia, and it led to the creation of new strains of plants that were better adapted to various climates and could feed more people.

But many questions remained open. It wasn't clear at all, for example, that human heredity followed the laws

discovered in plants. This question was much harder: people reproduced much more slowly than peas, usually giving birth to a single child at a time, and there was no way to organize their mating for a proper scientific study. Finding a trait linked to a recessive allele would be especially challenging. For it to appear at all in a child, both parents would have to carry it and pass it along, a situation which might be very rare. And if each parent carried both dominant and recessive alleles, like the first generation of Mendel's peas, only about a fourth of their children would exhibit the trait. That meant it might disappear for many generations, hidden by a dominant gene, and only reappear when the odds worked out.

Dominant traits ought to be easier to find because even if only one parent had a characteristic, about half the family's children would inherit it. But first scientists had to find human characteristics determined by single genes. It was easy to tell the difference between the colors of peas, or whether they were wrinkled or round, but what were the human equivalents? How many genes did it take to establish the color of eyes or hair, or build a

complex organ such as the heart? Scientists began looking for traits that were easy to recognize and distinguish from each other and that appeared in various forms. The first breakthrough came when a young American turned his attention to a family's short fingers.

In 1900 William Curtis Farabee was working on a doctoral degree in physical anthropology at Harvard University. It was a new field – he was the first student to receive the degree at Harvard, and the second ever at an American university – but one that had begun to bloom thanks to the theory of evolution. Darwin claimed that humans had evolved under the influence of natural selection and the environment. Discovering how that had happened would surely shed new light on human nature, but it would require observing humans in habitats similar to those in which most of their evolution had taken place. And it would demand measurements of fossil remains of hominids and related species, as well as variations in modern humans, which needed to be measured to trace the origins of our species and catalog the extent of its diversity.

Farabee was among the first of a wave of young scientists who traveled to distant regions of the globe to carry out systematic studies of human societies. Today he is known best for his exact observations – and a large collection of photographs – of the inhabitants of remote regions of South America. Since he was behind the camera most of the time, the collection doesn't contain many images of Farabee himself. One of the few shows him seated at a rough table in the forest, next to three colleagues, like a strange thesis advisory committee convened in the jungle. Farabee is the tallest, rake-thin, with a wide-brimmed safari hat that casts shade over his eyes.

He came to anthropological work with great respect for his hosts and a thoroughly modern attitude: "There are no primitive men, neither is there primitive culture," he wrote. Societies are inextricably bound to their environments, and they should not be studied without a thorough understanding of the natural setting. "Civilized" people were not somehow better than those of undeveloped countries; instead, they were equally products of the dialogue between their genes and the environment.

Today this is a fundamental principle of anthropology, but during the first decades of the twentieth century it was a contentious point. Notions of human evolution had become confused with ideas about progress and social change – perhaps "civilized" people represented more "advanced" stages of evolution.

This idea had a dark side: a widespread fear that "undesirable" members of society (as defined completely subjectively by various groups of rich and powerful people) might out-reproduce the ruling classes and thus somehow have a detrimental effect on the evolution of mankind. The notion was used as a justification for widespread *eugenics* programs which attempted to control human reproduction by mass-sterilizing tens of thousands of criminals and patients in psychiatric institutes. That happened very widely in the United States, and the Nazis used the ideas as an excuse for the Holocaust. Their efforts were nothing more than thinly-disguised racism, and they had about as much basis in evolutionary or genetic science as Mary Toft's stillborn rabbits.

The idea that Western cultures were somehow more evolved was also used to justify slavery, still a common practice in South America when Farabee made his expeditions. The anthropologist's feelings on the subject are best captured by his account of the family history of one of his translators. Simasiri, a native of the Macheyenga tribe of Eastern Peru, had been sent to live with a well-educated Spanish family as a young boy:

He spoke and read Spanish very well. A year before my visit he was taken back to the interior to serve as an

interpreter among his own people… He met one of his cousins who told him of the fate of his family. His father and mother had been captured and sent to different places down river; his sister had been dressed up and sold to a rubber gatherer; his brothers had been killed, and he alone had escaped…The Peruvian Government has since prohibited this slave traffic, and punished the offenders. I was delighted to see one of the worst offenders against this tribe carried away in chains for trial.

Farabee is best remembered for these long anthropological trips to South America, but the topic of his dissertation had been human genetics. The project began with his discovery of a family in Pennsylvania, whom he gave the pseudonym "Davy", who had unusual fingers. Those who were affected were fairly easy to identify, especially using a new invention called an X-ray machine. The pattern exhibited in their fingers was always the same: the four fingers of each hand were entirely missing one of the segments (called *phalanxes*) normally found between two of the joints. The thumbs had the normal number of phalanxes, but one was much smaller than the norm.

Otherwise, the Davy family seemed healthy. "The people appear perfectly normal in every other respect and seem to suffer very little inconvenience on account of the malformation," Farabee wrote. "The ladies complain of but one disadvantage in short fingers, and that is in playing the piano; they cannot reach a full octave and hence are not good players."

In some situations, short fingers might even provide people with an advantage – in Turkey I watched one of the family members pluck a hazelnut from a plate, curl his short, strong fingers around it, and crack the shell. When I tried to do the same thing, I couldn't grip it tightly enough; my phalanxes were too long. I had to resort to a nutcracker.

Farabee visited the Davy family, carried out measurements and conducted interviews that allowed him to trace the trait of short fingers back through five generations. He discovered that the feature strictly followed the pattern of inheritance expected for a dominant gene.

A long family legend supported his findings. The Davys claimed "…that the first person having short digits came from Normandy in the army of William the Conqueror, and remained in England; that persons with short fingers have never intermarried; that every other child born of a short fingered parent has short fingers; and that no long fingered descendant of a short fingered parent ever had short fingered children." The young anthropologist was skeptical about the story of the soldier – who would have lived nearly 850 years earlier – but the rest of the tradition pointed to a clear pattern of inheritance. The unique fingers of the Davy family were the product of a dominant gene.

Farabee had not only discovered a gene and alleles related to the structure of fingers – he proved that human heredity obeyed Mendelian laws. Later, he would encounter albinos among dark-skinned tribes of South America, and his analysis would suggest that the lack of pigment in their skin was due to a recessive gene. He had placed the first signposts along the path to a science of human genetics.

Kemal was undoubtedly disappointed after his meeting with Mehmet Sonel in Ankara, but he didn't stop trying to find help for his family. By 1964, headaches and other symptoms of high blood pressure were taking their toll and he was briefly hospitalized in Ankara. They tried to treat his hypertension with drugs such as diuretics, which cause people to pass more water in their urine.

"The idea is that there is too much fluid in the vasculatory system – like letting to much water into a garden hose without releasing it," Fred says. "In some forms of

hypertension this is an effective therapy, but in Kemal's case it had no effect."

Every year that passed would bring a worsening in Kemal's symptoms and a step closer to the fate of his relatives. He made one more attempt to find help, in the hospital in Samsun, closer to home – although the trip still required the long walk to the coast and a bus ride. He underwent an examination and talked to Mithat Veysoglu, a doctor who was interested in probing the family history. The next time he came, he would bring along his three brothers.

In purely scientific terms that trip would be more fruitful. Careful interviews with the brothers allowed the physicians to establish a pedigree – a diagram that showed who was affected and who was not, arranged in a proper family tree. The pattern that emerged resembled the one Farabee had produced for the Davy family: Kemal and his relatives were very likely suffering from a defect in a dominant gene. But in terms of the family's health, once again, this trip would make no difference at all. Veysoglu's paper appeared in in a Turkish-language journal that had little visibility outside the country. The report vanished into the literature as just one more peculiar case of a human hereditary disease that could neither be understood nor treated.

4 "Treasure your exceptions"

There is no single gene that determines the length of fingers, or the pressure of blood moving through a person's vessels. If the Turkish family had been found in the early twentieth century, however, a geneticist might have come to such a conclusion from their condition. Completely puzzling would have been the way a single gene might cause two conditions that seemed totally unrelated. In studying the family, Fred Luft and his colleagues have reaped the benefits of a century of genetic research into animals and humans.

Today we know not only what genes are made of, but also a lot about how they work. Part of that knowledge has been gained through a collision between the sciences of biology, physics, and chemistry. Another part has been gained through the careful study of the bizarre effects of mutations that may produce short fingers, or extra fingers, or much more dramatic effects such as an embryo without a brain.

Understanding the complexity of the problem faced by Kemal's family – and the group's efforts to define it – requires a trip back into the history of genetics and biology. "Treasure your exceptions," said William Bateson, the geneticist who made Gregor Mendel a household name. Bateson found a lot of exceptions in nature: bees with legs growing

where they ought to have antennae, animals with extra sets of horns, and human males with extra nipples. He described the study of heredity as "a class of research that calls perhaps for more patience and more resources than any other form of biological enquiry."

If there is a credo to Fred Luft's research, it consists of those two parts: "Treasure your exceptions," which he has instilled in every colleague who has ever worked with him, and a seemingly infinite patience. The same qualities in another scientist, Thomas Hunt Morgan, turned animal genetics into a truly modern science.

Two main problems confronted early 20th-century geneticists. The first was to identify the type of molecule that genes were made of – an effort that would mainly rely on physicists and chemists. The second was to discover how they functioned in complex organisms; here, answers would depend on finding an animal that reproduced quickly and prolifically and could be raised with ease in the laboratory.

The most stunning stride toward solving the first question was made by Francis Crick and James Watson. I had the mixed pleasure of meeting Watson more than ten years ago, in the quiet, wood-paneled office from which he directed the Cold Spring Harbor Laboratory on Long Island, in New York. Watson had played a crucial role in the establishment of the European laboratory where I used to work, which was coming up on its 25th anniversary, and I was there to interview him about its origins. Within five minutes he had insulted both the laboratory and its current director, so I abandoned the agenda, turned off my tape recorder, and decided to simply enjoy the company of a central figure in 20th century science. Once I realized that Watson said whatever came to mind, without any sense of political correctness, we had a pleasant chat. As I left, he gave me an autographed copy of one of his books.

The volume was mostly devoted to work that Watson had carried out in the 1950s with his colleague Francis Crick, and the vast panorama of science that had arisen from it. In 1953, in an article barely more than a page long, the two men exposed the structure of a molecule called DNA. Their double-helix model explained how cells copied genetic information as they prepared to divide; it also provided a tantalizing hint as to how mutations might occur.

While establishing once and for all that genes were made of DNA, the paper had deep philosophical implications. It seemed to finally settle a long debate on the nature of life itself. In a tradition stretching back to Newton and Galileo, the natural sciences had been defined by a *materialist* view of the world. This tradition maintained that the existence and behavior of physical objects – from stones, to living beings, to the universe itself – could be described in terms of physical and chemical laws. Given an initial set of conditions such as the Big Bang, the structure of matter, and a defined set of forces, natural laws could produce everything else. This didn't necessarily mean that everything could be explained, or that the world operated according to strictly determinist principles. It simply pushed anything supernatural beyond the domain of science. It claimed that supernatural explanations should not be sought if physical causes would suffice.

This contrasted with a *vitalist* world view which claimed that inanimate objects, including inorganic atoms and molecules, could never produce living beings. Bringing something to life, from this perspective, would require the infusion of some special, vital force that departed again when an organism died. Religious traditions generally held a vitalist view of things because it left the

door open for supernatural interventions: A life force might be spiritual rather than physical.

A century ago, this notion of a "life force" was still compelling enough to intrigue an entire generation of physicists. If it existed, they reasoned, it might be a physical phenomenon rather than a supernatural one. And if some special force was at work in living beings, the physicists wanted to know about it. You couldn't have a scientific explanation for the universe without including the biological world.

A number of physicists began looking at the significance of claiming that genes had to follow the same rules of chemistry and physics that governed the behavior of every other type of molecule. Many young physicists had been attracted to biology after reading a popular book called *What is Life?*, written by Nobel prize-winner Erwin Schrödinger. Its central ideas had already been expressed in the 1920s in an article by Hermann Muller. He was another Nobel laureate whose work showed that exposure to X-rays triggered spontaneous mutations in the fruit fly and other animals. There's a direct connection to this story: For a brief period in the 1930s, Hermann Muller worked in a building on the campus in Berlin-Buch, a stone's throw from where Fred Luft has his office today. The two men have given lectures in the same room – six decades apart.

Yet Schrödinger's book is an example of popular science writing that captured the imagination of Watson, Crick, and other future Nobel Prize-winners – including a young physicist named Max Delbrück – and motivated them to join the search for the gene.

As a result, some of the major figures of early 20th-century physics turned their attention to biological problems. They quickly found that methods from that branch of science could be used to investigate life. Newly-invented X-rays, for example, could be used not only to examine the insides of bodies, but also very small objects like molecules. Visible light has a very broad wavelength, which restricts its resolution – seeing objects beyond that range would be like trying to play a Chopin etude on the piano while wearing boxing gloves. The waves of X-rays are much narrower, which permits discerning points that lie closer together, provided those objects are arranged in a regular, repeating structure like a crystal or a fiber. (You can hit single keys of a piano – which, interestingly enough, are also arranged in a consistent structure – because they are designed to fit the dimensions of normal fingers.)

William Bragg and his son (William) Lawrence Bragg developed a hypothesis about X-rays and the atomic structures of crystals that provided a means of analyzing and interpreting the structures of several chemical compounds. The two men shared a Nobel Prize in Physics in 1915 for this work, making the son (at 25) the youngest person ever to receive the honor.

Lawrence went on to have a prestigious career that greatly influenced the development of biology. He set up the Cavendish Laboratory at the University of Cambridge, where Watson and Crick would do their work on DNA. He had such a significant impact on science that he was knighted and became head of the prestigious Royal Institution in the United Kingdom.

His research career was accompanied by a passion for gardening. When he moved to London and had to abandon his beautiful garden in Cambridge, he scoured the neighborhood for one in need of care. He approached a homeowner who lived a few blocks away and offered his services one afternoon a week, introducing himself simply as "Willie." The lady of the house remained unaware of his identity until a guest looked out the window one day and said, "Good heavens, what is Sir Lawrence Bragg doing in your garden?"

DNA had the structure of a fiber, so in the 1930s and 40s William Astbury of the University of Leeds started stretching DNA fibers and shining X-rays through them. His work was continued in the early 1950s by Maurice Wilkins and Rosalind Franklin at King's College London. The images they obtained revealed the circumference of the DNA double helix (although they didn't know it had this shape at the time) and the distance between the "steps" of this winding-staircase structure.

Through contact with Wilkins, Watson and Crick got a glimpse of Franklins' X-ray work and it gave them crucial information in figuring out the architecture of the DNA molecule. Since she hadn't published the data, many consider this to be an act of scientific misconduct; she might have come up with the structure of DNA herself. (It's important to note that even if she had, she wouldn't have been awarded a Nobel Prize for her efforts, at least not in 1962; the prize can only be given to living scientists, and she died of cancer in 1958.)

The chemical building blocks of DNA had to fit the parameters of Franklin's measurements. The process was like assembling a puzzle out of the chemical subunits of DNA, called *nucleotides*. The scientists had their machine shop make metal forms that they tried to fit together until the double helix took on the right shape. After many attempts, one afternoon Watson realized that snapping the *guanine* (G) shape onto that of *cytosine* (C) produced the same basic shape of an *adenine* (A) attached to *thymine* (T), and that they fit into the circumference dictated by the X-ray studies.

Max Delbrück's role in this story is also peripheral but interesting. He never worked directly on the campus in Berlin-Buch, but had interactions with scientists working there; together, they made another important contribution to the search for the chemistry of genes. In the 1930s Delbrück was working as an assistant to the nuclear physicist Lise Meitner in Berlin. He organized a set of scientific lectures at his house in Berlin-Grunewald, to the south of the city. One of his early guests was Nikolai Timoféef-Ressovsky, a Russian immigrant working at the Kaiser Wilhelm Institute for Brain Research. The institute had been created in the 1920s and was the first research organization on the Berlin-Buch campus.

For his first talk at Delbrück's house, Timoféef-Ressovsky spoke on Muller's work on mutations in fruit flies. The Russian and his colleague Karl Zimmer were discovering that larger doses of radiation increased the number of mutations that flies experienced. Delbrück and his new biologist friends began considering the implications of this effect – they believed it shed light on the chemical and physical structure of genes.

If the units of heredity were arranged in a linear way on chromosomes – as the German scientist Wilhelm Roux had suggested many years before – then X-rays would probably strike them at random points. If they hit a gene, this might disrupt its chemistry. That meant that the dosage experiments might be helpful in calculating the size and potentially other features of genes. The units of heredity were beginning to take on a tangible form.

The three men collected their ideas in a booklet that became known as the *Green Pamphlet* – for the color of its binding – which became nearly as widely known as Schrödinger's work. It was another inspiration for Watson and Crick.

Delbrück's association with science in Berlin-Buch had another effect: The institute that Fred Luft joined in the 1990s was named after him.

Neither *What is life?* nor the *Green Pamphlet* answered a basic question: what type of molecule were genes made of? Scientists had begun focusing on structures inside the cell nucleus that looked like fuzzy snippets of yarn. These vast knots of molecules, called chromosomes, dissolved and reappeared as cells passed through cycles of rest and replication. They came in pairs, always assumed the same shapes when they reformed, and were divided into single copies in egg and sperm cells. They paired up again during the fertilization of the egg. This looked compellingly like a mechanism whereby each parent could contribute information to its offspring.

Wilhelm Roux had proposed that genes might be located on chromosomes, and that the information they contained might be in linear form, like a text composed of letters and words. That concept would take over fifty years to demonstrate, but it was a place to start: it might be possible to link a particular trait to a single chromosome.

But when you extracted chromosomes from cells, you ended up with vast numbers of molecules called proteins. It also left you with a much more basic molecule called *deoxyribonucleic acid*, or DNA. It was hard to imagine that the simple chemical "language" of DNA, with only four "letters", served as a recipe to build an organism. Proteins were spelled with a twenty-letter alphabet of amino acids, and were regarded as much more likely candidates.

It would take several decades for the scientific community to shift its attention to DNA, eventually culminating in the model proposed by Watson and Crick. But even so, at the dawn of the 20th century, genetics was about to take a gigantic step forward.

Over the next few decades, significant insights into the functions of genes were gained largely through the efforts of a researcher named Thomas Hunt Morgan and several generations of young scientists who cut their teeth in his lab. The first time Morgan's name came up in a discussion with Fred Luft, he told me, "Did you know he was the nephew of the famous Confederate General – John Hunt Morgan?" Revealing, once again, the extensive encyclopedia of science history and trivia that Fred carries around in his brain. It took me too long to realize that this wasn't simply a symptom of a mind that likes history. Most scientists float forward on a line of research without looking at the deep currents that are responsible for carrying it along. Very few scientists impart a sense for history or culture or their importance to students, but Fred is one of them.

Morgan received his training in the 1890s, before Mendel's work had resurfaced. Neither Darwin nor anyone else had the slightest clue as to how organisms transmitted features to their offspring, or how changes in those features could arise.

It's amazing, in retrospect, how much Morgan and his colleagues learned about genes and their structure with the tools at hand. When Morgan began setting up his laboratory at Columbia University in New York in 1907, he had a few microscopes and a hypothesis about heredity that he didn't find fully convincing. But over the next few decades, his lab's excruciatingly careful studies of a tiny fly led to a revolution in the science of genetics.

Morgan was a die-hard skeptic who rarely took the work of other laboratories at face value, often repeating their experiments himself before accepting their conclusions. He doubted Darwin's hypothesis that natural selection was the main cause of evolutionary change, that Mendel's principles of heredity were equally applicable to animals, and whether genes were really located on chromosomes. When close colleagues proposed that one pair of chromosomes – named *X-Y* for their shapes – was responsible for determining the sex of an organism, he doubted that as well.

I think that Thomas Morgan and Fred Luft would have hit it off famously – for their healthy skepticism in the face of established theory, for their willingness to follow a line of research in the absence of clear hypotheses, wherever it might lead, and most of all for a quality of seemingly infinite patience.

Morgan began thinking of ways to observe evolution in the laboratory. One of his sojourns abroad had been spent in the lab of Hugo de Vries in Amsterdam; de Vries had developed the concept of "mutations" – random changes in the genetic code – as the source of variation in species. It was an intriguing idea, one that Morgan felt might be testable in the laboratory.

However evolution worked, everyone agreed it was a slow process – but "slow" could mean different things. If you had the right organism – one which reproduced quickly and was easy to care for in the laboratory – perhaps you could catch it in action. Morgan began thinking of ways to accomplish this. The problem was, most genetic work focused on plants. The reasons were largely practical: plants didn't leave messy cages to clean and they produced a lot more offspring than animals.

Franz Lutz, a collaborator from Harvard University, recommended the fruit fly. The insect reproduced just two weeks after birth and had lots of offspring. It could be kept alive on a diet of mashed bananas. And it had just four pairs of chromosomes – so if those structures were, in fact, the home of genes, it would be easier to find them in an animal that didn't have too many. (Humans, by comparison, have 23 pairs.)

So the new laboratory quickly became a facility to breed and investigate fruit flies, in hopes of observing mutations and, hopefully, evolution. No one knew how long you'd have to wait to find mutations that might produce a new species – it might take decades, or centuries. Even Morgan might have been considering writing the project off in frustration. But the more flies they looked at, the more they became used to the details of a normal fly, and suddenly in 1910 the effort paid off. Morgan noticed a slight change in the color patterns on some of his insects' bodies.

At that point the floodgates opened, and mutations seemed to appear everywhere. The first really dramatic find was a male fly whose eyes were white rather than the normal red color. If this represented a mutation, the trait ought to be hereditary, so Morgan bred the fly to produce a second generation. Some of the males and females in the next generation had white eyes. So far, so good: the patterns could be predicted according to Mendel's principles. Then he began crossing them with normal flies, and the result was chaos.

When red-eyed males were mated with white females, the male offspring all had white eyes and the daughters red. But reversing the roles, and mating white-eyed fathers with red-eyed females, produced a first generation that all had red eyes. If those flies were mated, a quarter of the males in the second generation had white eyes. Mendel's rules were working, in general, if you supposed that the sex of the insects was somehow skewing the results.

Morgan's colleague and former mentor Edmund Wilson proposed a solution: the gene for eye color might be located on the X chromosome. Females had two copies of any genes located there (because they had two X chromosomes), and males had only one – which they inherited from their mothers. As chromosomes are divided, sperm receive one chromosome from the X-Y pair from their father. If they are to produce males, it must be the Y chromosome, and so the new fly has to receive the X from its mother.

Somehow a single copy of the mutant gene gave males a trait that did not appear in females. Wilson suddenly realized the same phenomenon might explain something he had observed in human inheritance. He was extremely

color-blind, arousing his curiosity about how this trait passed through the generations of families such as his own. His observations suggested that it was passed from mothers to sons. The same pattern emerged in hemophilia and a number of other diseases: The genes that were responsible might lie on the X chromosome.

A month later another mutation linked to sex appeared in Morgan's lab: wings that grew to only about half the normal length. More mutations appeared, and some followed the same pattern. Elizabeth Wallace, a researcher and talented artist, discovered a mutation that gave males yellow bodies. Another created vermillion-colored eyes. She painstakingly documented the changes in a series of paintings that became renowned for both their beauty and scientific accuracy.

Morgan began a tradition of naming genes after the effects of mutations. For example, he called the gene that led to white eyes "white", although the function of the normal version of the gene was probably to create red eyes. The genes for mutations that changed the size and shape of the wings were called "miniature" and "truncate".

By 1915 the lab was working with dozens of mutant strains. The focus of the work was steadily shifting from evolution to the discovery of new genes and working out aspects of their behavior.

One thing that slowly became clear was that one of Mendel's cardinal principles – that genes were inherited as completely discrete "packages" – wasn't absolutely true. Some traits tended to accompany each other in the offspring at a rate much higher than chance association. As time went on the lab discovered additional traits that seemed to lie on the X chromosome; these, for example, were almost always passed down together.

But there were exceptions to this rule as well, and one of Morgan's students came up with a possible reason. Alfred Sturtevant had been thinking about the way chromosomes were divided up as reproductive cells were made.

Thomas Morgan

When a Belgian researcher named Frans Alfons Janssens watched this happen under the microscope, he noticed that the strands of chromosomes were twisted around each other, making sharp bends.

Morgan thought this pressure might make the two strands break at parallel sites. Cells had to have some way to repair them – otherwise, most eggs and sperm would inherit fragments that rendered them infertile. In the process, pieces of the neighbors might be exchanged, and genes might be transferred from one chromosome to another. Morgan called the hypothetical process *crossing-over*; today it is known as *recombination*. The idea had important implications. It meant that mothers do not pass down entire, intact X chromosomes to their daughters.

The information in each chromosome is remixed with each generation.

Up to this point, Morgan had considered genes rather abstract ideas, like the variables in an algebra equation. It made little difference what they were made of, as long as they behaved in a predictable way. The discovery of recombination was about to change that.

Sturtevant suddenly realized that recombination could help identify the physical locations of genes on chromosomes. His reasoning went something like this: Suppose that genes were like words that appeared in a few very long sentences (the chromosomes). Each mutation discovered by the lab affected a word. Making a gene map would be like trying to reconstruct the sentences. Fortunately, the words didn't come completely separately and randomly, but in blocks – genes that were inherited together, on the same chromosome.

Crossbreeding the mutant strains showed which words "belonged to the same sentence," and their overlap would allow scientists to assemble groups into much longer ones. To take the metaphor further: Suppose that the sentences were printed over and over on long strips of paper. Recombination was like cutting each strip at a random place. Statistically, words close to each other on a strip would tend to stay in the same segment when it was cut. Words much farther apart – separated by greater distances on the chromosome – were more likely to be separated.

Sturtevant collected Morgan's data showing the frequency at which genes were inherited together. Working at home, in a single night he managed to plot the positions of six genes. The map showed their order on the chromosome and gave a relative idea of their distances from each other.

This procedure was easiest for the X chromosome, but the group quickly moved on to others. By 1915 they had plotted 36 genes on four chromosomes. By 1926 the map included 36 genes on one chromosome alone.

All of them had been discovered according to the principle of "treasuring your exceptions:" finding a healthy gene required the discovery of an exceptional fly.

Over several decades, Morgan's lab at Columbia University and later at the California Institute of Technology, where he relocated in 1928, discovered mutation after mutation in fruit flies, identifying genes that would turn out to have close relatives in humans and other animal species. In the process, they discovered some other types of changes that DNA undergoes as chromosomes recombine, divide, and recompose the pairs needed by a new organism.

Calvin Bridges began his scientific career washing bottles and preparing food for the flies in Columbia. His colleagues soon became aware that he had a knack for laboratory work: He came up with the idea of anesthetizing the flies with ether to make them easier to sort, and using watercolor brushes to split them into groups on porcelain plates. When he discovered an interesting mutant with brightly colored eyes, Morgan gave him a desk and brought him onto the scientific team.

One of his first discoveries revealed that, in very rare cases, traits located on the X chromosome were not inherited in the expected way. White-eyed females should produce only white-eyed sons when they mated with red-eyed males. But about one in a thousand of their offspring had red eyes. Bridges called this event *nondisjunction* and interpreted it correctly: Sometimes egg or sperm cells received two copies of the sex chromosome, or none at all, rather than one.

The huge numbers of flies and strains and careful accounting managed by the Morgan lab kept producing sta-

tistical anomalies such as non-disjunctions. Bridges had a talent for figuring out what they meant. First, he discovered that entire subsections of chromosomes completely disappeared – a female might lack a piece of one of its X chromosomes. The group's gene maps made it possible to identify the positions and sometimes even estimate the size of these missing pieces. They could range from a piece of a single gene, to a block containing several, to an entire chromosome. They could be detected using statistics – as variations in normal patterns of Mendelian inheritance.

Next, Bridges discovered that pieces of chromosomes containing one or more genes were sometimes duplicated. This helped explain one of the mysteries of evolution: Animals had different numbers of chromosomes, and humans surely had more genes than bacteria or simple one-celled organisms. Where had the extra material come from? Showing that flies sometimes acquired extra copies of genes – and sometimes of entire chromosomes – offered a possible answer.

Within two decades the lab had discovered hundreds of genes, but their work was limited by the fact that they had to wait around for genetic mutations to occur naturally. And none of the scientists had any idea of the total number needed to make up the fly. Morgan once estimated it to be about 2,000, which turned out to be a severe underestimation. With the completion of the Drosophila genome in 1999, the number turned out to be about 14,000.

Even if the figure had been closer to 2,000, waiting for natural mutations in all of them would take a long, long time – and many would escape detection anyway. Any gene that was really crucial to the early stages of fly development, for instance, would kill the embryo, leaving nothing to look at. In fact, any mutation that rendered a fly infertile would be useless for genetic studies. The only way to ensure that a trait was the work of a single gene was to watch the offspring of a mutant fly for enough generations to ensure that it followed Mendel's laws.

The 1930s, however, saw a dramatic increase in the pace of discovery. Hermann Muller, another visitor to Morgan's lab, had moved to the University of Texas. A focus of his new lab was to find ways to increase the rate at which mutations occurred. He began using radiation, which caused the number to rise dramatically. But it was tricky business: exposure to X-rays and radium usually sterilized the flies. Eventually the technique was worked out by manipulating dosages, one point that Max Delbrück, Nikolai Timoféef-Ressovsky, and Karl Zimmer picked up for their proposal about the nature of genes in their *Green Pamphlet*.

Muller's work demonstrated – among other things – that exposure to radiation could be harmful to human health. As he was immersed in this work, it claimed the life of the great Marie Curie in 1934, robbing her bone marrow of the ability to produce new cells. Other scientists who worked with radiation – for example, physicians – started to take precautions, and to protect their patients. Then, of course, two atomic bombs were dropped on the cities of Hiroshima and Nagasaki, bringing along an immense risk of genetic damage to survivors and their future children. This brought home the importance of research into radiation, and just a year later, in 1946, Muller was awarded a Nobel Prize for his work on the topic.

Muller had always had an uneasy relationship with Morgan, due to disputes over the authorship of publications produced by the lab. In some cases he had contributed to work but had failed to receive what he considered to be appropriate credit. Tensions reached a high point in the 1930s with a discovery about genes that took place simultaneously in his lab and that of Morgan at Caltech.

Theophilus Painter, working under Muller in Texas, had discovered that cells in the salivary glands of flies contained giant-sized versions of chromosomes. These were so large that they offered an unprecedented look at chromosomes under the microscope, and Painter began staining them with dyes. Each chromosome had a characteristic shape, and he discovered that it had recognizable sub-features as well. When stained, dark bands of various thicknesses appeared. They reappeared in the same places each time this was tried, and there didn't seem to be any significant variation from fly to fly.

This was of huge interest to the gene mappers: It might give them a way to pinpoint a gene's precise location on a chromosome. Until now, all the maps had shown positions in a relative, statistical way. But it hadn't been possible to point at a specific place on a chromosome and say, "This gene is located there."

Homing in on a single gene would require a landmark, and Calvin Bridges (who had moved to California with Morgan) knew of a gene that might provide one. Years before, Morgan and Alfred Sturtevant had discovered a gene they named Bar because mutations gave the flies thin, rectangular eyes. In some insects the effect was mild; in others, it was very strong. The scientists assumed that in the dramatic cases, flies had inherited a second copy of the mutant gene. It was located on the X chromosome, and Bridges had calculated its relative position.

Now he extracted cells from the salivary glands of flies with the Bar mutation. He studied them carefully under the microscope and discovered the pattern of chromosome bands was slightly different in normal and mutant insects. In flies with the narrowest, most-slot-like eyes, that region was duplicated.

Muller happened to be in Russia at the time, where he was carrying out exactly the same experiment, and coming up with the same results. Being abroad delayed his ability to publish the results. A dispute erupted about who deserved credit, particularly since the key discovery had been made in Muller's lab. Both sides felt strongly because the discovery was incredibly important: In just a few experiments, the men had proved that a gene's physical position could be pinpointed, that duplications of genes had occurred, and that having two copies of a gene influenced the way the eye developed.

And there the work got stuck – the scientists still didn't know what a gene was made of, which left them in the dark as they hoped to understand its effects on cell chemistry and ultimately the formation of complex structures such as eyes or wings. Even the most basic answer to those questions had to wait until the 1950s, and then figuring out the details would become a central topic in science for several decades.

That work goes on, in one form or another, in most molecular biology labs today. It's the central issue in the study of genetic diseases. Understanding the way genes and other molecules produce a healthy body is essential if you want to figure out what has gone wrong in a mutation. And vice-versa: the changes that mutant animals undergo can reveal the healthy function of genes. On the flip side of every healthy gene can be found one of its variants – sometimes deadly, sometimes just inconvenient. And in rare cases, a mutation might be beneficial.

It's a type of thinking that arose from Morgan's lab at the beginning of the twentieth century, and it's what has made a Turkish family so important at the beginning of the next one.

The pathway that links a gene to its ultimate effects on cells and organisms is a tremendously complicated story, and working out its details have been a main focus of molecular biology ever since James Watson and Fran-

cis Crick proposed the double-helix model of DNA in 1953. Their work the machine-like structure that allowed the two strands of DNA to bind to each other and replicate themselves. George Beadle and Edward Tatum had already established a crucial point of gene function: that genes encode proteins. If you inherit a defective form of a gene, you are unable to produce the protein that corresponds to it. But even this great insight failed to explain how DNA could be "translated" into proteins.

The four nucleotide bases of DNA form the "steps" of the double helix; sugars and phosphates are attached at the circumference, creating the "rails". What made genes different from each other was like what distinguishes two pages of text written in English. At the most basic level, you could count how many times each letter of the alphabet occurs on one page and compare the results with the numbers from another page. But what *really* counts is the linear order in which the letters are arranged; the same alphabet can be used to say completely different things.

The same principle holds for the nucleotide bases of genes. Except that the chemical alphabet of DNA has only four letters, and it's a very, very long text. The chromosomes in a single human cell consist of about three billion pairs of bases. Hidden in that information are over 20,000 genes, and each has its own spelling. (Unless your genome contains a recent duplication, like the Bar mutation found in fruit flies, which could produce two identical genes.)

Somehow cells could translate this four-letter alphabet into another chemical code: the richer, twenty-letter alphabet of *amino acids* that make up proteins. Francis Crick began to take a closer look at the question, and he soon proposed a new model – which he called the "central dogma" of molecular biology: "DNA makes RNA makes protein." In other words, the information in a gene was first transformed into a similar molecule called RNA (in a process called *transcription*). This newly synthesized molecule provided a template, a sort of recipe book, telling the cell how to select the right amino acids and string them together in the right order to build a particular protein.

Crick's "dogma" had a number of implications that took many years to prove. There was no direct way to translate a four-letter code into a system with twenty letters. To choose the right amino acid, a cell would have to be able to interpret strings of at least three nucleotides in an RNA molecule. Scientists began trying to link various combinations of three letters (called *codons*) in RNAs to specific amino acids. It took the efforts of many labs to crack the code. The solution gave them a sort of bilingual dictionary: the sequence of amino acids in a protein, listed in their proper order, could be connected to the sequence of nucleotide bases in the gene that had produced it.

The dogma also offered an explanation for the way hereditary information – or defects in it – could affect cells and organisms. Experiments carried out across the world were revealing an increasing number of functions for proteins. These molecules helped ingest nutrients and process them into raw ingredients for the cell. They passed biochemical signals from the surface to genes. They created pipelines to carry molecules from one location to another, and fibers that gave the cell its shape, and on and on. Ultimately, a cell's form and behavior could mostly be explained by reference to the proteins that it produced. Proteins carried signals from one to another, setting up a system by which tissues could receive vital information from their surroundings. Such signals told new-born cells that they were in the brain and should develop into neurons, or that they should become muscle, blood, and all the other tissues in the body. They explained why information in an imaginal disk to create one color of eye, for example, could be overridden by information from surrounding tissues.

So the dogma accounted for many of the effects of mutations. Spelling changes in the DNA sequence of a gene could change the spelling of an RNA. That might introduce a small change in the chemistry of a protein, making it unable to carry out its functions, or eliminate the molecule altogether. That could have potent effects on a cell, changing its shape, its ability to specialize, or its proper integration into a tissue. In the ensuing years scientists learned that the loss of a single protein could produce an animal without a brain, or with other serious defects in its body.

Other problems could arise because a gene might be completely lacking, or stem from the duplication of part of a gene or a larger region of a chromosome – as Calvin Bridges and Hermann Muller had discovered. A second copy of a gene might lead to the production of twice as many proteins, and quantities were surely important.

Through work on *Drosophila,* other laboratory animals such as mice and rats, and human patients, scientists began to trace many more diseases to defects in genes. One day, they hoped, they would be able to zoom in on gene sequences, compare their "spelling" in various people, and pinpoint specific errors that made people ill.

A machine that could accomplish this wouldn't be invented for another twenty years. But while it wasn't yet possible to directly read the information stored in DNA molecules, researchers kept coming up with creative ways to explore the nature of genes and their effects on cells. Sometimes they used technology that was absurdly simple and close at hand. One breakthrough, for example, came from a machine sitting right on the kitchen shelf. And it landed there because a clash between the cultures of French cuisine and the American kitchen.

The structure of the DNA molecule showed how it might be copied, and how mutations might arise: sometimes, as one of the strands was used to make a new one, the wrong nucleotide might work its way in. But this didn't explain most features of the behavior of genes: for example, how the genetic code in a fertilized egg cell could be used to spin off cells with a wide range of shapes and behavior.

Some of these details began to emerge through work carried out at the Pasteur Institute in Paris by François Jacob and Jacques Monod. The two men complemented each other perfectly: Jacob seemed to have an intuitive grasp of how cells worked, and Monod's talents lay in breaking down complex problems into steps that could be tackled in single experiments.

Jacob and his colleague Élie Wollman were interested in a curious phenomenon that had been noticed in bacteria. These single-celled organisms passed on genes to their offspring by dividing. But sometimes they appeared to spread genes in another way, by donating them to their "brothers and sisters." This seemed to be a form of mating, but the idea was controversial.

Then Jacob managed to prove it using an ordinary kitchen blender. He had bought it during a trip to the United States, a culture in which appliances to make life more comfortable – by easing the burden of cooking, for example – were appearing all the time. He intended it as a gift for his wife. She took one look at it and declared that such a device had no business in a French kitchen, so he took it to the laboratory.

Jacob and Wollman grew male and female bacteria in isolation from each other. To demonstrate that the cells could mate, they had to force a gene to move from one population to the other. They began with females that had a defective form of a gene called *lac B*. The function of this molecule was to help bacteria break down milk sugar into two parts called galactose and lactose. Bacteria could survive without the gene, and you could measure whether they had it by exposing them to milk sugar and

observing whether they broke it down. They used male bacteria with a working form of lac B, and then waited to see whether it would be imparted to the females.

The process of transfer, called conjugation, was very slow. It might last as long as two hours, and that fact led to another interesting discovery: If mating was interrupted in the middle, only some genes were transferred. It was different than the all-or-nothing fusion that occurs when plants or animals mate, which requires pairs of chromosomes to be split apart and recombined into a new set that is original, but must be complete. In bacteria, the longer mating went on, the more genes were transferred, always in the same order.

Jacob discussed these findings with Monod and the two men came up with the "spaghetti hypothesis" of the transfer of bacterial genes. A bacteria's chromosome might be like a long strand of spaghetti, containing genes in a specific order, which was slowly pushed from the male to the female. If this process was interrupted, the strand broke off and no more genes were transferred. To stop the mating, you simply had to shake the bacteria apart – in the kitchen blender.

If this idea was correct, there had to be some type of physical transfer of the "spaghetti", and maybe it could be seen under the electron microscope. A close look at mating cells revealed that they were connected by a tiny, string-like bridge. Its function was to move DNA from one cell to the other.

Because the process was so slow, the scientists could interrupt mating at precise times. This broke the chromosome at specific places, and it allowed Jacob and Wollman to make an exact map of the positions of genes on the chromosome. It was a bit like recording a conversation and then transcribing it. You start the recording, stop it to write down what you have heard, and then start it again to listen to the next part.

"DNA makes RNA makes protein," Crick said, but genes don't do so all the time. Recent studies have shown that a given human cell, for example, only produces about 20 percent of the proteins encoded in its genome at any given time. In complex organisms this permits the creation of different types of cells: different sets of proteins give cells different features and behavior. It also permits cells – including bacteria – to respond to changes in the environment by switching genes on and off. When food gets scarce they activate molecules to respond to stress; if levels of acid in the environment rise, they adjust their internal chemistry to cope. They produce different molecules to adjust to heat, cold, dryness, and other changes that they have faced before and have evolved to cope with.

What determines the status of a specific gene? Jacques Monod originally supposed that its normal state was "off", and that something – probably a protein – was needed to switch it on. Experiments soon showed that he had it mostly backwards. Bacterial genes were usually stuck in the "on" mode, a state in which they would produce proteins all the time. If they were silent, it was because control molecules were acting as brakes. To create a protein, the brake had to be released. Monod and Jacob called these control molecules *repressors*. They were probably proteins, and they probably carried out their jobs by attaching themselves to DNA.

This meant that in addition to a protein-coding region, a gene had to be associated with extra control regions. These were probably DNA sequences close to a particular gene where proteins docked and controlled its activity. Jacob and Monod called these sequences "operators." They probably weren't genes themselves, because they didn't hold the information necessary to create a protein; instead, their function was to receive a signal.

If the receiver was broken, no signal would arrive, and a gene would be unable to respond when the cell tried to change its activity. Experiments showed that this was exactly what happened when a mutation changed a gene's operator. In 1960 the scientists modified their definition into the concept of the *operon*: a structure in genes that contained both genes and their controlling regions.

Soon the scientists discovered that operons had even more parts. At the beginning came a *promoter* region whose job was to attract an *RNA polymerase*: the molecule that actually reads a DNA sequence and uses it to build an RNA molecule. (A polymerase is a general term for an enzyme that builds other molecules by gluing together smaller units.) Promoters for different genes would have different features that depended on what was happening in the cell. When a lot of a particular protein was needed, the promoter for its gene should be chemically very attractive to RNA polymerases. Genes needed in small quantities had less attractive promoters.

The next segment of the operon contained the operator. If the brake was "on", a repressor might sit there and act as a physical barrier when the RNA polymerase tried to slide down the gene. The polymerase would be derailed, leading to either an incomplete RNA or none at all, and no protein.

Monod made one more important hypothesis to explain how a protein might activate a gene. It might latch onto a repressor molecule and pull it away, giving the polymerase access to the gene.

The work of Jacob, Monod, and many others had now provided a much fuller view of the gene. It was now seen as a complex "operating platform" where many other molecules could meet to alter the gene's output. This platform could be disturbed by a mutation in any functional region – the promoter, the operator, the protein-encoding section, and other regions yet to be identified. At the beginning of the twentieth century, Thomas Hunt Morgan had described genes as abstract entities – like variables in the algebra of life. Now they were complex, chemical structures with many functions. A mutation that disrupted any of them could lead to disease.

So by the mid-twentieth century, researchers had pinned down the physical basis of genes and demonstrated that they had their effects by producing proteins. And the functions of those molecules could be explained in a completely materialist way. Mutations changed the architecture of proteins in a way that altered their normal functions in cells. Understanding a problem like short fingers and hypertension required following the flow of information from a gene to a protein and figuring out how the change disrupted the normal state of affairs. Finding exceptions had become the guiding principle in understanding conditions of health and disease.

5 The mule that climbed a family tree

By the age of 39, Nihat Bilginturan had already led a life more colorful than most of his colleagues could ever dream of. After starting his medical studies at the University of Istanbul and completing them in Ankara, he received a fellowship to travel to the United States, where he received three more years of training at the Children's Hospital of the Harvard Medical School in Boston. Following his return to Turkey, he carried out two years of obligatory military service, and had finally attained a dream position: Medical Director of the Hacetteppe Children's Hospital in Ankara.

As one of Turkey's most prestigious centers of medical care and education, the hospital has had a huge responsibility to bear since construction began in 1957. It began as a children's hospital and has maintained an emphasis on child care throughout its history. Located inland, in the high central plains of the North, Ankara is the only major city within a radius that, in some directions, extends for over a thousand kilometers. Its hospital provided the only advanced care available, in most cases, for a population of millions scattered throughout most parts of the country.

Directing the hospital entailed many administrative duties, but Nihat Bilginturan continued to see as many patients as he possibly could, and his colleagues knew to call

him in on special cases. He hadn't been there long before a family showed up in his examination room. At first the attention was focused on their one-year-old child.

"I examined him and detected a first- and second-degree heart murmur," Bilginturan says. "The X-rays showed a normal heart size, so we discussed that for a while and talked about the child's needs. As I was discharging him, I noticed something about his family. His mother and the man who brought him in were short, stout, and had unusually short fingers."

The man was Kemal, and he had accompanied his cousin Mutabeer to the hospital with her child. It had been nearly ten years since he first sought help for his family; nothing had come of it. This seemed to be someone who would listen.

"He told me that in addition to these features, the family had a history of very high blood pressure," Bilginturan says. "Many of his relatives were affected this way. And they all died around the age of 45 from cerebral incidents. My two visitors were about to walk out the door but I said, 'Please, sit back down.'"

Out of habit and curiosity, he took the adults' blood pressure – obtaining the same astronomical results as the doctor who had first examined Kemal several years ago. Now he was truly intrigued. His interest in genetics and biochemistry had been stimulated during his time in the United States – devoted partly to patients and a year of research. He had never heard of a condition like this one. He might be looking at a genetic disease that had never been described in the literature.

Before the family left, he took their contact details. "I will need to come visit you," he said. "I don't know when, exactly, but we should try to make it soon. At that point I will need to examine every member of your family."

This could be done, Kemal assured him, feeling an excitement that he hadn't experienced in years. Ankara had what might be the best hospital in the country, and this was an important man. Maybe, finally, someone could help.

Nihat Bilginturan is a born storyteller. I met him in the lobby of a hotel in Ankara in late 2009. He arrived by taxi and entered the hotel, a thin, straight-backed man in an impeccable suit. I'd seen him in photographs taken over a decade ago. He'd aged – grey had taken over his hair, his glasses looked a bit thicker, and he'd lost some weight. He was having some trouble with his voice – undoubtedly the result of a series of recent operations on his esophagus and throat. Now in his late 70s, Bilginturan was losing some of his force. But over a three-hour period he leaned forward in his seat and his eyes gleamed. Every question evoked a new story that he was eager to tell.

His account of his first visit to Karamat, the village where Kemal and most of his affected relatives lived, made clear the adventure of serving as a physician in rural Turkey during the 1960s and 70s.

Several months after he examined Mutabeer's child in Ankara in the spring of 1970, Nihat Bilginturan and a colleague boarded a bus in Ankara headed for the coast of the Black Sea. His companion was the hospital photographer, who would document the family's short fingers and other physical characteristics. Between them they had a considerable amount of equipment: cameras and a tripod, rolls of film, and a box of medical supplies for carrying out examinations. And each had a suitcase with enough clothes to last for a week.

The ride took several hours along a curved road, seeming to descend all the way from the high plains down to the foothills at the border of the sea. The arid plains gave way to a hilly landscape of lush vegetation and trees. Towns were few and far between.

Along the way it started to rain, lashing fiercely at the windows. It had slackened off by the time they arrived, but the city appeared battered and pools of water collected everywhere. The waves on the sea were choppy underneath a grey sky and rolled over the stony beaches with a grinding sound.

"When we got off the bus at the station, I told a man there that we had to go to Karamat. He said, 'That's impossible, there's no taxi or car.' I said I didn't understand; what was the problem? He told me the road wasn't good."

Bilginturan asked whether someone had a four-wheel drive vehicle that could make the trip. The man looked doubtful. "Well, maybe you can ask at the hospital; they have one."

So, lugging their equipment and bags, Bilginturan and his photographer made their way down the road to the hospital. There they encountered the next obstacle. Yes, they were told, there was an all-road vehicle. But its use had to be approved by the doctor; there was only one on duty, and no one knew where he was.

A half-hour wait stretched into 45 minutes. Finally Bilginturan's patience began to wear thin. "We have come all the way from Ankara, and we must get to our patients in Karamat." Finally the physician, Dr. Ibrahim, arrived. Once he heard the situation, he sent for the hospital's driver.

"His name was Selahattin," Bilginturan says. (He seems to remember the name of everyone he has ever talked to, over the course of several decades.) "The minister told him to take us to Karamat. He responded, 'I won't go there. I'll *quit* before I have to drive up there.' Finally the physician gave up and told us, 'All right, get in. I'll take you myself.'"

They climbed into the four-wheel drive vehicle and the minister began driving up the road. It was tough going: rain had collected in the ditches and ruts; mud slid down the embankments in a thick gruel, and water coursed across the path as it twisted and turned at random intervals. Even today, in dry weather, navigating the roads to the village is a task, and that's on a bed of dry gravel.

But that day they reached an absolute impasse. Halfway along the route the road had simply vanished in a mudslide. It was still raining heavily and the wheels of the vehicle lost their grip on the road. Bilginturan and the photographer jumped out and pushed until they managed to get the car turned around. It left them splattered in mud but no closer to the village. They decided to wait out the rain in the car before heading back.

"As we sat there, a man came by with a mule," Bilginturan says. "I asked where he was going, and he said he was headed for Karamat. 'Maybe you can help us,' I said, and I explained our problem. 'Please tell the Hafiz he has to come back and pick us up, and he should bring a couple of mules.'"

Their helper asked, "Where are you going to stay in Karamat?"

Bilginturan told him the name of their host.

"Oh, that's impossible; he's a poor man. You should be my guest instead."

It was a kind offer, typical of the hospitality that would be offered again and again by the family and their neighbors, but Bilginturan couldn't accept. He had exchanged letters with the family and agreed to stay a week; to change plans now would be an insult. So they sent the man off to find the Hafiz.

It meant another long wait in the car. "After a couple of hours," Bilginturan says, "the Hafiz appeared on the back of a mule and leading two others. We loaded everything onto the animals and were finally on our way to the village."

Their helper hadn't exaggerated the family's condition. "The house had one bedroom and a big kitchen where

the family stayed, ate, made bread – they did everything there," Bilginturan says. "There was one very small extra room near the entrance, an open space used for heating. That's the cramped space where we were to stay for a week."

In the morning their hosts served breakfast, producing a loaf of bread, margarine, and jam. "Don't you have corn bread?" Bilginturan asked, knowing this was the staple of the family's meals. "And butter?"

Of course, came the reply – "But we didn't think you'd eat it."

"And honey?" The family raised bees and harvested the honey.

Again the reply: "You'd rather have honey? Of course, but we thought you'd prefer jam."

The men finished their breakfast and Bilginturan brought out his pipe to smoke. His host seemed anxious.

"When you're finished, your patient is ready."

"Which patient?" Bilginturan asked.

"*All* of them."

When they went outside, he nearly dropped his pipe.

"You've been to this area," Bilginturan told me. "You know that the houses are scattered – often 500 meters apart, separated by fields and the hills. Well, the day before, knowing that we were about to arrive, everyone left their fields, donned their best clothes, and headed toward Kemal's house. When we went outside, 30 or 40 people were standing there."

Across the terrace stood a small prayer house where a table and chairs had been set up for the examinations. Bilginturan took everyone's heart rate and blood pressure and did a routine medical workup. He spoke to each patient and then painstakingly recorded the familial relationships on a chart. Then the photographer took their pictures.

"By five or six p.m. I had finished with everyone – the whole family," Bilginturan says. "We went into the house for dinner. As we ate, I said, 'Hafiz, I have to leave tomorrow.' He looked at me in shock."

"You can't go," Kemal said. He produced the letter Bilginturan had written. "You said you would stay one week."

Bilginturan explained that he thought it would take that long to finish his work. "I never guessed we could accomplish it in one or two days."

Kemal looked at him and said, "Yes, and it might have taken a whole month. But this is what you wrote, and you have to stay a week!"

After a discussion – a long one, Bilginturan says – they finally settled on three days.

During the visit an encounter took place that would have a dramatic effect on the life of Kemal and his family, and would eventually change the fortunes of many other people in the region.

Kemal's older brother, Mehmet, came by in the evening and the men spoke over dinner. Bilginturan asked how the family made their living. Mehmet said that their entire income came from harvesting corn. The family ate it and used the shucks to feed their cow and the other animals. What was left over could be sold. But since so many other families did the same thing, maize brought a miserable price, leaving them continually on the brink of absolute poverty.

"How much does an acre of corn bring you?" Bilginturan asked.

Maybe 500 Turkish lira, Mehmet replied.

"What could you earn from growing tea?" Bilginturan asked.

About 5,000 lira.

"I was astonished," Bilginturan says. "I asked him, Why not tea, instead?"

Mehmet thought for a couple of minutes and then said, "But if we grow tea, what will we eat?"

"You could sell the tea and buy corn," the physician replied.

Another minute of pondering.

"But if we do this, what will we feed our animals?"

"You sell the tea and buy feed for your animals."

"No one ever suggested that," Mehmet said, and he remained thoughtful for the rest of the evening.

Five or six years later, Bilginturan says, he was working in his office at the hospital in Ankara when Mehmet appeared at the door. The two men hadn't had any contact during that time, and his visitor had suddenly appeared, out of the blue.

"I've come to take you to Karamat," Mehmet said.

"Excuse me?" Bilginturan said.

"I'm a rich man now, and I have built a cottage on the seaside. It is very nice there. I want to invite you and your family and children to come spend one month there."

"I can't leave my work for a month," Bilginturan laughed. "I might be able to get off for a week."

"Then you should come for a week," Mehmet said.

A short while later, Bilginturan and his family accepted the offer. As they drove toward the coast, they noticed a considerable change: Many of the rolling hills that had hosted high fields of corn were now carpeted by low, dusky bushes of black tea and hazelnuts.

After Bilginturan and the photographer spent their obligatory three days in Karamat, they made their way back to the coast – the roads had not yet been cleared, and once again they had to rely on the mules. Over the following weeks Bilginturan worked up the data he had collected from the family. A talk with a geneticist at the hospital made it clear that to be sure they were looking at a genetic disease, he would have to create a complete pedigree – a family tree showing who was affected and who was not – for Kemal's extended family.

The work allowed Bilginturan to close in on the history of the problem. He concluded that six generations previous to the youngest affected child, a woman had arrived in Karamat from a village farther to the east, bearing the condition. He could not determine whether she was the founder – in other words, whether it had originated in an initial mutation that had occurred for the first time in her own cells. She might have inherited it herself, which meant that there could be other relatives in other parts of Turkey who were likewise affected. So far none have been found. But somewhere in another remote village, another

family and their doctor might be puzzling over the same strange problems that Bilginturan had found.

What Bilginturan could determine, however, was that all of those affected in Karamat were descendants of this one person. What he had done so far convinced him he was dealing with a genetic disease and that it was a dominant disorder: Anyone inheriting the DNA sequence involved, wherever it lay, would exhibit the symptoms of short fingers and high blood pressure. This also told him that the syndrome could not be cured. The best that could be hoped for was to treat the symptoms, and at the time, there were few truly effective treatments for high blood pressure.

In fact, Fred Luft says, "In the 1960s we had thiazide diuretics and reserpine, which as treatments weren't that bad if you could achieve the proper doses. The problem was at the time it hadn't been proved that lowering blood pressure really helped anybody. Doctors called the type of hypertension this family had 'essential hypertension,' because they believed that the high pressure was essential to shove blood through diseased vessels, which offered a resistance."

So at the time, Bilginturan was limited to offering a single piece of advice. "If you want to stop this disease, I told them, anyone who is affected shouldn't get married. They said, 'Are you crazy? Of course we are going to get married.' I told them, 'Well, then the only thing to do is not to have children.' Again they looked at me as if I were crazy. 'It's not worth it,' they said, 'We'll just have to accept the fact that people die at 45 or 50.' There was nothing to do, and I returned to Ankara."

6 A sleepwalking Ummahan

Nihat Bilginturan's next efforts regarding Kemal's family came a few months later, when he decided to have a closer look at the family's hypertension. He had five affected family members brought to Ankara, where they were admitted to the Internal Medicine ward of Hacettepe hospital. During their stay they were X-rayed and underwent a broad range of tests. But nothing revealed a physiological reason for their high blood pressure.

That wasn't particularly surprising given the fact that today, about 25 percent of the population of industrialized countries (and increasingly throughout the rest of the world) suffers from hypertension. Even today, the causes remain a mystery. At the time, there was virtually nothing Bilginturan could do for the affected family members. It left him feeling helpless; unless a treatment could be found, early death would continue to sweep its path through the affected family members.

What he could do was tell the world. Bilginturan summarized his findings in a scientific paper entitled "Hereditary brachydachtyly associated with hypertension," which was published in the September 1973 issue of the *Journal of Medical Genetics*. There it would languish for nearly 20 years. But appearance in an important journal ensures that a piece

of science remains on library bookshelves and is recorded in such a way that it can be found. There a huge number of unresolved scientific puzzles are still waiting for a new insight or a technological advance that will permit them to be cracked.

Today that's easier than ever thanks to the Internet and the fact that journals are published in electronic form. Resources like PubMed, a database and website managed by the National Center for Biotechnology Information in the United States, gives instant, global access to any article that has been published. Currently there are so many laboratories throughout the world working on major questions that it often takes a researcher hours of reading every week to keep up with a molecule that interests him.

PubMed provides access to virtually any piece of work that has been published throughout the world, over the past thirty or forty years. This reduces redundancy in science; research labs quickly become aware of work going on in their area, either through publications by other scientists or the talks they give at major conferences. It also means that an arcane piece of work published decades ago may be dug up and assume a central role in a new project.

In writing his paper, Bilginturan was well aware that he had run up against the limits of current genetic science. On the other hand, he had taken the most important step: making the world aware of the family's problem. One day their time might come.

Over the next two decades, Nihat Bilginturan often thought back on Kemal and his family. There were few opportunities for direct contact, except for the invitation to spend a week on the coast of the Black Sea in Mehmet's new cottage.

And then, in 1978, Turkey held elections to choose a new Prime Minister. This occasioned another visit from Mehmet, Kemal's brother, who had come to stay with relatives in Ankara. Mehmet appeared in his office one day for advice.

"Dr. Bilginturan," he said. "We don't know what to do. Please tell us what party we should vote for."

He was a bit taken aback. "I'm working for the State," he said. "I can vote, but I'm not permitted to give you any advice."

Mehmet, however, was not deterred. He had brought along a copy of the Qur'an and opened it helplessly. "Nobody knows what to do," Mehmet said. "Please, we need help. We don't know which party is the best."

Hedging, Bilginturan stated the name of one of the parties. "I don't know how much better they are," he said, "but most people expect them to win."

In the end, everyone voted for the party he had named.

"Everyone in the village?" I asked him, three decades later.

Bilginturan laughed. "Everyone in the entire region!" he said.

Bilginturan had plenty of other things to occupy his mind. When we met, he was happy to talk about his experiences as a physician both abroad and for many other rural Turkish families.

Soon, for example, he became enmeshed in another project involving another village and another genetic disease, and in this case his involvement would save several lives.

That adventure began with another arrival in the clinic. A man came to visit with a disturbing story: his wife had borne 13 children. All of them had died before the age of six months, and some even before reaching one month of age, of high fever, seizures, vomiting, and diarrhea. Now

his wife was pregnant again, expecting to deliver soon. "Can you help save this child?" he begged.

Bilginturan said he would do whatever he could. "We admitted the mother and I examined her. I talked to one of our biochemists who did an analysis of her blood, but at first glance he didn't find anything. This was an excellent colleague, very dedicated, and he ended up spending all night in the hospital as the baby was born. He took blood from the umbilical cord, from the mother and child, and rushed it to the lab.

"Just before the delivery we found a publication describing a condition involving an enzyme deficiency, which bore some striking similarities to this case," Bilginturan said. "During a postmortem investigation of the child who had died, they found a deficiency in an enzyme called *leukocyte acid phosphatase*. Now the blood tests showed us that both this mother and child were suffering from the same deficiency. The only treatment was to administer prednisone, which the body could convert into the missing enzyme, and it had to be done regularly, over a long period. We ended up keeping the infant in the hospital for a year before we felt comfortable discharging him." The man and his wife named the child "Yasar" (which means "alive"). Their second child was born with the same problem, but was saved by another stay in the hospital and the new therapy. This time the baby boy was named "Nihat".

A talk with the father revealed that many other families in his village had similarly suffered; an astounding 45 families had lost 10 or more children. It sounded like another genetic disease; well, he'd already had some practice. Once again he set off for a distant region of Turkey to try to uncover its nature and origins.

This time he decided to establish the pedigree right away, and he sought out one of the oldest men in the village. "He was 75 or 76 but couldn't give me more information than just the last couple of generations," Bilginturan says. "I needed more. So he told me about a much older woman – truly ancient, he said – who lived there. 'She knows everything,' he said.

"'How old is she?' I asked. He looked at me. 'Well, she was already 100 years old when I was a child, so that makes her at least 160 or 170!'" In other words, she was an *Ummahan*, the Islamic equivalent of "Methuselah".

Bilginturan couldn't help the expression of disbelief that crossed his face. But the man insisted.

"At *least* that old," he affirmed. "And she can tell you just what you need to know. But… she's a little difficult. You have to be careful with her."

The man called her on the phone and said he had a visitor that she should meet.

"What for?" she said, suspiciously.

"He needs to know something about the village, and the families living here, and you are the oldest person alive."

She was still suspicious, but cautiously agreed to meet them. The man took Bilginturan to her home. By the time they knocked on her door, she seemed to have changed her mind. "She was a very large, formidable person," he reports. Did she look like she could be over 150 years old? "She looked very old," he admits.

She immediately chased them away. "Do you have an order from the court that I have to see you?" she screeched, and the two visitors fled.

"Well, the word got out that a doctor had come from Ankara," Bilginturan says. "So the next morning about a dozen people showed up with various complaints. Sometime during the day the old woman showed up and nosed her way into the line.

"You say you're a doctor, but I don't believe you," she said. "Maybe you can prove it to me. I have a pain, here, in my back." She pointed to the spot – or tried to.

Bilginturan sent his assistant for his bag, and when the man returned, he gave her an aspirin. "Take this," he said. He talked to other patients for a while and she returned after half an hour with the proud announcement that the pain was gone. Maybe there was something to be said for doctors after all.

Still, he noticed, she seemed remote to the point that he doubted he would get what he needed from her. "Do you have any other complaints?" he asked.

"Yes," she said, "But there's nothing you can do."

"Tell me."

One of her relatives stepped in. "She walks in her sleep."

"Excuse me?" Bilginturan asked.

"In the middle of the night. She doesn't know it. She gets up out of bed, starts walking up the hill, and then she gets to the top. She wakes up without knowing how she got there and has to walk all the way back down to her house."

There was no way to treat sleepwalking, Bilginturan knew, but then he had a sudden inspiration. The problem was most likely psychological, and here he might draw on one of the most amazing and mysterious products of medical science: the placebo. He found a package of calcium tablets in his bag. Dissolved in a glass of water, one of the tablets produced a strange, orange fizz that bubbled on the surface.

"Drink this just before you go to bed," he told her. "And tonight, the ghosts will be unable to take you up the mountain."

Very early the next morning he was sleeping soundly when there came a rude knock at the door. He opened it to find the woman standing there. "I was afraid she'd come to beat me up," he says. But no; she was overjoyed – she hadn't walked in her sleep and was anxious to tell him about it.

"Come back at 7.30," he told her. She wasn't happy and grumbled, but she turned to go home.

Another inspiration: "Tell me what you like for breakfast," he said.

"Eggs cooked in butter," she said. "And tea."

After squeezing in a couple of more hours of sleep, Bilginturan rose, went to the market, and bought twenty eggs and a kilogram of butter. He took them to her house. She wasn't awake yet, so he left them just inside the door.

Later, when he returned, he found her rested and content in the wake of a good night's sleep and a hefty breakfast. She was in such a good mood that she answered all of his questions, providing him with a thorough pedigree of six generations of the history of the town's inhabitants.

"I never found out her true age," Bilginturan confesses. "But everything she told me about the relationships within the families – over all of that time – turned out to be accurate. And the pedigree that we developed became an important tool in diagnosing the families at risk and helping to avoid this terrible infant mortality."

In 1973 Bilginturan flew to Brussels where he gave a presentation at a meeting. Afterwards, he says, one of the attendees, named Dr. Robert Jackson, approached him.

"I'm working at the University of Missouri and will retire one year from now," he said. "I was tremendously impressed by your talk. Can you come to the university and take my job?"

Bilginturan was surprised, to say the least. "I don't have a Green Card," he said, referring to the visa that foreign nationals must have when they work in the United States.

Ali praying

Getting one was an intensive process that usually took months.

"I'll get you a Green Card in a week," the man said.

"How?"

"Don't worry about it."

"Well, if you send it, I'll come."

Ten or fifteen days after his return to Turkey, Bilginturan received a phone call from the American embassy in Ankara. They were holding a Green Card issued in his name.

"So I packed up my family and we went to Columbia, in Missouri," Bilginturan says. "I took my sabbatical and we stayed there for two years. It was a very nice place, and we had a good time."

Asking for his impressions of the United States triggered a series of stories that evokes his personality as well as any of his scientific adventures do.

"You know, the very first time I went to the U.S. I was in Philadelphia," he says. "The first day I went to the student cafeteria, where they were serving pork chops. They knew I was coming, and that I was a Muslim, so they had gone to a lot of effort and made a special menu for me with chicken."

He was disappointed. "I'd actually prefer the pork," he said. And so they sent the chicken back to the kitchen and gave him the normal menu.

He didn't know anyone except his boss, "Dr. DiGeorge," he says, and sat down at the table with him. He introduced Bilginturan to a colleague, another member of the staff of pediatric nephrology, who was surprised at the meal on his plate.

"Dr. Bilginturan, you're a Muslim!"

"Yes," Bilginturan said.

"But you're eating pork, and you're not supposed to!"

"Yes, I am a Muslim, but not a strict one."

The new fellow looked at him sternly. "No, you are a Muslim. There is no such thing as 'strict' or 'loose'. You're a Muslim and you're not supposed to eat this."

Dr. DiGeorge had followed the conversation with some amusement. He turned to Bilginturan and said, drily, "Why don't you ask our friend here why he's eating pork? He's a Jew!"

Later, when Bilginturan met Dr. Jackson at a conference at Columbia, the scene repeated itself virtually verbatim in the cafeteria – this time, however, the topic was beer. Bilginturan had asked for a good Missouri beer.

Dr. Jackson told him, "But you're a Muslim! You're not supposed to drink."

"Yes, I am a Muslim, but not a strict one – I can drink beer."

Bilginturan later learned that his colleague had worked in Lebanon for a couple of years, where he learned about Muslim traditions. And Jackson's father had been a very strictly religious Jew who believed that you should follow the rules of whatever religion you adhered to.

More amusing stories came from Bilginturan's work ethic.

"In Missouri I had to start working at eight a.m. and often didn't finish until seven or eight in the evening. Then if I had to do something in the lab, I might stay until midnight. After a month or so the department chairman approached me and said, 'Dr. Bilginturan, your contract says that you should do 70 percent research and 30 percent teaching.' I wasn't supposed to come in every day at eight a.m., and if I did, I should feel free to leave at four p.m. or so. If I had additional work to do, I could do it at home."

Bilginturan protested that he liked the work and wasn't asking for additional pay.

"No, no," the chairman protested. "We can't pay you more because you're not an American citizen."

Bilginturan repeated that he didn't want any additional pay.

"Well, perhaps I can give you one or two days of private practice so that you can make more money."

No matter how hard he tried to explain that his behavior wasn't a subtle way of demanding more pay, the chairman kept trying to help. One day he arrived and said, "Dr. Bilginturan, I have a form in my hand. I want you to fill this out. It will allow us to give you 400 or 500 more dollars a month. Please, please accept this!" So Bilginturan filled out the form.

He stayed in Columbia for two and a half years; the contract ended in the middle of the year. He asked if he could stay another six months so that his children could complete the American school term. The university accepted; they even wanted to offer him a long-term contract. Bilginturan was interested, but he said he could only accept if he was granted tenure. That went against university policy – professors had to have been at the university a certain number of years before they could be considered for tenure – so the offer didn't work out. "Otherwise I would be an American now," he says.

During his entire time at Columbia, he didn't take any vacations, with one exception when his mother-in-law came for a visit. The family met her in New York, where Bilginturan was attending a meeting on endocrinology, and he added on some extra time to take the family to Canada and Niagara Falls. Upon his return the department chairman once again showed up at his office in a state of distress.

"Dr. Bilginturan," he said, "Except for these two weeks, you haven't taken any vacation!"

Bilginturan said he knew, but he hadn't needed or wanted to take time off.

"That's impossible – you must take the allotted time off!"

"I don't want to," Bilginturan said helplessly.

"But you must!"

In consternation, the chairman left. Later, as Bilginturan was wrapping up the formalities to return to Turkey, he received a check from the department.

"It was for 6,000 dollars!" he laughs. "They felt they had to pay me for all the accumulated vacation time I hadn't taken."

In the early 1980s, Bilginturan saw an announcement in the *New England Journal of Medicine*: King Faisal University in Saudi Arabia was looking for physicians with various areas of specialty: medicine, surgery, pediatrics, and so on. He applied and was called to Dahrein for an interview. After a talk with the dean of the medical school, he was practically hired on the spot.

Bilginturan eventually spent four years in Saudi Arabia, helping establish the new medical school. But at the end of that period he wanted to leave – this time, his family had stayed behind in Ankara. His children were in college in Turkey, and he had been gone too long. He gave notice punctually, according to the rules: you had to submit your resignation three months before the contract expired.

His colleagues were distressed. The dean visited his office and said, "You know there are rules about salaries, but if you aren't happy, we can increase your pay."

That wasn't the problem, Bilginturan said; his family was in Ankara, and he'd been gone a long time.

The next visit came from a family practitioner with strong connections to the royal families and the university administration. "We understand you are returning to Turkey," he said. "You simply can't go."

Once again, Bilginturan tried to explain.

"Why don't your children come here?" the man said. "Whatever they want to study, whatever subject, they can study here. Your son can come and we will give him a scholarship." Again, Bilginturan politely refused.

The next day he received a phone call that an important visitor was waiting in the lobby of the department. He went out and found the Vice-chancellor of the university. Once again, an offer was made: full scholarships for any of his children who wished to attend. He promised to consider the situation, but he would have to discuss it with his family first, and he could only do that in Ankara.

"So I escaped," Bilginturan laughs. "I don't know what they would have offered if I had waited any longer."

In 1994, the extended stays in the United States and Saudi Arabia and years of work at Hacettepe Hospital had relegated Kemal's family with their problem of short fingers and hypertension far to the back of Bilginturan's mind. Then, after a twenty-year hiatus, something happened that would bring the story back to life in full force.

"One day I was contacted by a polite young medical student from Germany, of Turkish descent, representing a certain Professor Luft in Berlin," he says. "He told me that Professor Luft and his colleagues had read my paper with interest and now, perhaps, had the facilities to make it possible to discover the gene. If I wanted, we could make a joint study."

Bilginturan had recently turned down a similar request from a French laboratory, and within days of Hakan's visit yet another letter arrived – this time from a group in the United Kingdom – making virtually the same proposal. They, too, had discovered the paper. Bilginturan wrote a polite response turning them down. "I told them I was already collaborating with a group in Germany," he says.

Fred Luft and Hakan Toka

7 Culture shocks

Friedrich Luft was born in 1942 in Berlin, a grand city steadily being hammered into the ground by Allied bombers. The night skies screamed in an unnatural dialogue between the Earth and the heavens, carried out in a language of tracer bullets, flares, the drone of sirens, the blasts of cannons and bombs, and the fumes of smoke from fires. Fred's father was working abroad, and by 1943 the situation in Berlin had clearly become too perilous for an infant. Fred and his mother were evacuated to the other side of the country, to a town along the Eder Valley. As it turned out, they were moving out of the frying pan and into the fire.

His new hometown and the region soon achieved a dubious sort of recognition, Fred says, thanks to an Allied attack launched on the night of May 16, 1943. The Ruhr region was crucial to the German war effort. Energy for the Ruhr was largely supplied by hydroelectric power from the dams; leveling them, the Allies knew, would be a crippling blow. But the dams were heavily defended: Anti-aircraft guns strafed the night skies, and any torpedoes dropped by bombers would be blocked by a series of sophisticated nets. The sharp hills on either side meant that a plane would have to dip into the valley, navigate through fog and slip past German guns to make a pinpoint strike. A dam was a narrow target to hit from a quickly moving plane. To have any chance of success, a normal raid would

probably require hundreds of planes, and most of them would be lost. The cost was too high.

The Allies found a creative solution by developing in a barrel-shaped bomb that could be dropped by a low-flying aircraft, spin backwards in a way that made it skip across the water like a whirling stone, and smash into the huge concrete walls. Around midnight of the 16th, nineteen planes flew out of Scampton, in the United Kingdom; only nine would return. In three waves they entered the airspace of the Continent on the coast of the Netherlands, descending to an altitude of about 30 meters to avoid enemy radar as they swept over the countryside. During the actual strikes they had to fly even lower, skimming a mere 18 meters over the river at high speeds.

The attack successfully punched huge holes in the Möhne and Edersee Dams. About 330 million tons of water rushed through the breach on the Möhne and flooded the areas downstream. The rush of water caught the population unawares, and about 1,600 people were killed. Factories and mines were flooded; houses, bridges, roads, and railway lines were swept away. Eight thousand cubic meters of water per second flowed through the hole in the Eder dam. As a result, an eight-meter high flood wave moved down the Eder valley. The result was devastating. "My grandmother's house was a sturdy three-storey stone structure, about 15 kilometers downstream," Fred says. "Water didn't reach the third storey."

The strike was dramatized in a book called *The Dam Busters* written by Paul Brickhill, a British airman who had been held by the Germans as a prisoner of war. (Brickhill is best known for *The Great Escape,* a book about his experiences at Stalag Luft III.) Both works were made into popular films. A flight sequence from the film version of *The Dam Busters,* in which pilots swerve into the valley and zoom down the narrow river while evading enemy fire, is said to have inspired a similar scene at the end of the movie *Star Wars*.

Fred and his mother survived the night – and most of the rest of the war – within the safe, dry walls of a sturdy Hessian farmhouse. In 1945 they returned to Berlin, but not for long. "My father was struggling to get some work done at the Charité – tough going right after the War," Fred says. "Then he got an offer to work in the United States, in San Antonio, Texas. He headed off under the auspices of a somewhat shady governmental program to snap up German scientists, probably mostly to keep them – and their work – from falling into the hands of the Russians. A year later my mother and I followed."

The family joined a huge wave of German emigrés headed for the U.S., and Fred and his mother were finally reunited with his father in San Antonio on Thanksgiving Day. But to make their entry official, they had to undergo a complicated procedure involving taking a bus to the Mexican border, crossing into the neighboring country on a bridge, and then walking back again. "The Army was hoping to fudge the numbers by making it seem like all these immigrants were Mexicans," Fred says. "It was called 'Operation Paperclip,' and it was the method used to get Werner von Braun and an assortment of other German scientists into the United States."

By the time he and his mother returned from the Mexican border, it was time to start thinking about finding a school. Within a few minutes on the first day of grade school, he realized that his teachers would probably forever mangle his first name. They couldn't make the gargling sound to produce the German "r", didn't know whether the first vowel should be pronounced like the letter "e" or "i", and seemed incapable of properly landing on the soft "ch" at the end.

Outfitted with a shorter name that everyone could pronounce, Fred set sail into the American school system. As in every other classroom across the country, starting from the first day, he and his classmates had to learn the "Pledge of Allegiance," an oath of loyalty. They

would repeat it at the start of every school day for years and years. The class stands, with hands placed on hearts, and earnestly recites:

I pledge allegiance to the flag
of the United States of America,
and to the Republic, for which it stands,
One nation, under God, indivisible,
with Liberty and Justice for all.

Like many other first graders, Fred didn't know what all the words meant. He did know, however, that there was a fancy store downtown called Joske's Department Store. "It was founded by German immigrant Julius Joske in 1867. It eventually became a national chain, but the first store was there in San Antonio." So when he came to the last line, he called out proudly, "with Liberty and Joske's for all."

"To the great amusement of everyone," he says.

After a year or two, you could barely tell him from most other kids in his Texas classrooms from the way he talked. Most children can become "native speakers" if they move to a new language culture before they reach their teens. But it didn't hurt that English was his father's first language, and Fred had been speaking it with him since he had learned to talk.

Over time he fit in most other ways as well, but adaptation had its price: he was losing his memories of Germany and his ability to speak the language. His mother was particularly determined that he remain fluent and learn to read and write properly. That would be difficult since there were no German courses in grade school and that was also the case in many high schools. So learning the language became the first item on the agenda evenings and weekends, surplanting any plans with friends. He had a personal tutor – his mother – who did her best to ensure that German remained the language at home. Spending hours examining the nuances of irregular German verbs was not his idea of a good time, but his mother got her way.

"She still corrects every mistake I make in German, with an astonishing precision and vehemence," Fred says. "Sometimes she adds a comment like, 'If you'd only tried harder back then!'"

Correcting his papers gave his mother practice for later, when she taught German and Russian at the University of New Mexico. Fred never saw the papers she returned to her students, and he wondered what kind of comments she might give them. Would she accuse them of being too lazy to learn in grade school, as well?

Fred says that he had a "close but formal" relationship with his father and only later realized how much the man had been a mystery to him. After his father's death, Fred found an application for tenure to the Charité university hospital in Berlin. The form had been submitted it in 1941, only to have it promptly returned with a terse comment: *Rejected on the grounds of political unreliability.*

Establishing an identity is an issue for every emigré, even a young one, and it was a particularly thorny issue for Germans in the post-War years. Discovering that his father had run afoul of the Nazis was like finding a certificate that he'd been a "good German."

"I was tremendously proud of that," Fred says.

One of the great unifying themes of this book is a confluence of cultures. On the scientific front, this has taken the form of the coming-together of basic biological science and patient-oriented medicine. It has yet to be achieved on the grand scale that scientists and physicians envision. But there are many other examples. Even within the life sciences, it has taken decades for fields such as genetics, evolution, and biochemistry to come together. One point of contact is the cell, and the study of the way

a single fertilized egg develops into a fully-formed organism such as a human being. At even lower levels, physics and chemistry are becoming intertwined as researchers work out the relationship between a single molecule's atomic structure and its functions.

This grand unification in biology is occurring thanks to the advent of incredible new technologies – able to capture a view of the entire DNA sequence that makes up an organism's genome, and to catalogue the entire population of RNA and protein molecules produced in a cell. Researchers can follow the subtle biochemical changes that transform a generic stem cell into any of the hundreds or perhaps thousands of types that make up a human being. It's a crucial step in describing the transformations that sometimes go awry to produce conditions such as cancer or genetic diseases. The technologies produce immense amounts of data that are utterly dependent on computing, mathematics and its daughter field statistics. Making sense of biological processes requires new methods of modeling them. Even very basic problems, such as understanding how a string of amino acids folds into a single protein, are so complex that they probably could not yet be solved even if every computer in the world were devoted to them full-time, at full capacity.

But the effects of the revolution have already been felt in many ways, for example by transforming our classical definition of disease. Sometimes syndromes have been lumped together under one name due to the fact that they cause similar symptoms in the body. Scientists anticipate that this process of classification and renaming diseases will continue for a long time. It is due to a massive import of tools from chemistry and physics and computing into biology. With a much more refined view, researchers have been able to peel apart conditions that look similar into distinct entities. Every individual is genetically unique (with the exception of identical twins); modern studies are now permitting better diagnoses and treatment, targeted to specific conditions, and a better understanding of how a person's genetic background contributes to side effects.

Apart from such collisions within the scientific culture, there is the international aspect of research. Virtually every scientific story crosses borders – diseases don't respect the political lines drawn across the world map. Research itself is an international enterprise; every study builds on an immense amount of data and knowledge collected across the globe. Scientists themselves come from all walks of life, from all nations and ethnic backgrounds. It makes no difference where someone is raised; science is a universal language that is spoken across the globe, and it is carried out in a way that is supremely democratic. Politics does play a role, but that mostly happens at the level of science policy and education. There is no Politburo standing at the top of everything to promote one type of work and dismiss others. A single person working in a lab can make a discovery that requires everyone to rethink what he is doing.

But there is no guarantee that a project which crosses national borders will be easy to carry out. Particularly when the research involves patients; you can't get a license to practice medicine in every country.

Even though science is a globally democratic exercise, the individual still plays a huge role: personalities, an individual's culture and style of thought, and his or her motivation are crucial ingredients in the recipe. This story reflects the fact that sometimes, success requires a collusion of people from different backgrounds, who happen to be at the right place at the right time, in a particular political environment, with specific interests and motivations.

As German-born Friedrich was becoming American-raised Fred, the land he had left began pulling itself out of the ruins, through economic aid and strict oversight

from the occupying forces. Anyone able-bodied – veterans, housewives, retirees, and children – helped clear the streets of rubble and start the process of reconstruction.

Rebooting German industries required labor, and the war had left the country in a dire situation. At first immigrants from the East filled the vacuum. But that source dried up with the construction of the Berlin Wall. A new invitation was extended to southern countries, and treaties for guest workers were arranged with Italy, Spain, and Greece. Then in 1961 the German government signed an agreement with Turkey to allow workers to come to Germany on two-year permits. Eventually the number of people with Turkish citizenship – including workers, their families, and their children – would reach 2.5 million, making this the largest immigrant group in the country.

The two-year limit on the length of stays quickly turned out to be an illusion. Many immigrants had come in hopes of earning higher wages and returning to Turkey to start their own businesses, but two years rarely sufficed. Germany was happy to have them because the country still needed the skilled laborers. After extended stays, many of the immigrants had brought their families into the country. They began having children who were born and raised in Germany; most entered German schools and had little contact with their parents' home country, except for visits during vacations. After several decades of residence, many finally acquired citizenship through a relaxation of German law.

Among the Turkish families who took advantage of the workers program were the Tokas, whose father worked in an automobile factory in Munich. The two sons, Hakan and Okan, went on to fulfill a family dream of studying medicine and becoming physicians. The young men were to become central figures in this story when they joined Fred Luft's lab in the 1990s.

And one branch of the family of Kemal and Cafer settled in the southern German city of Stuttgart, bringing along the DNA for short fingers and hypertension.

A few years after his arrival in America, Fred Luft's family settled in Albuquerque, New Mexico. There his father was appointed director of the Lovelace Institute – responsible for training the seven astronauts for the first American spaceflight program, called "Mercury". "It meant that I got to know all of the astronauts, went skiing with them, and followed their adventures with awe," he says. "Before a flight, each of them gave my father a good bottle of Scottish whiskey which he was only allowed to open when the astronaut safely returned to Earth. Fortunately, he got to open all of them."

That luck didn't hold; later, as Mercury evolved into the Gemini and Apollo space programs, one of the men suffered a tragic accident. Gus Grissom, whom Fred had known, burned to death with two fellow astronauts during a practice test of the Apollo 1 spacecraft.

Fred had received his high school diploma in 1960 and decided to study biology in Colorado. Following medical studies in Philadelphia, he received a position as an intern at the University of Indiana, whose medical school lies in Indianapolis. "After a couple of years of working 80- to 100-hour weeks," he says, "I was promoted to Chief Resident."

At the time, he says, his head was stuffed with information: he'd learned the textbooks on internal medicine by heart and subscribed to all of the important medical journals. "I knew about everything there was to know at the time – probably more than I remember today," he says.

On the practical side, however, there was still a lot to learn. One day he was examining a patient who appeared to be suffering from liver disease, brought on by years of


Verbandkasten

excessive drinking. After examining the man's chart, Fred noticed the indication of a slight fever. He decided to perform a routine extraction of fluid from the man's swollen belly. This involved inserting a thin needle carefully into the abdominal cavity. Fluids accumulate there for a variety of reasons, and their analysis can be important to detecting a problem.

In the days before ultrasound, the procedure was accompanied by a slight risk of penetrating something else – for example, the intestine. Fred watched in horror as a grey-white liquid filled the chamber of the syringe. "I knew what it was," he says. "The day before, the patient had undergone a procedure involving barium; it was still in his intestines, and right away I knew that's what I was seeing. I'd punctured his gut."

A serious wound to the intestine could result in poisonous wastes leaking into the abdomen, almost inevitably causing peritonitis, sepsis, and death. Fred quickly withdrew the needle and ran down the hall to the head of the section, the patient and a nurse staring as the door slammed shut behind him.

He entered the office in tears – only to find that he had burst in on a meeting of section heads. The senior physician, John Hickam, couldn't help noticing that something was wrong and immediately sent everyone out of the room. Fred calmed down long enough to explain what had happened. The experienced doctor listened to what he said and nodded solemnly.

"It was a stupid mistake, but you don't have to worry," Hickam told his young colleague. "The needle you used is so thin that there won't be a leak and the wound will heal itself in a day." Then he regarded the young doctor carefully and added an afterthought. "Don't use medicine as an excuse from living," he said.

Fred didn't immediately appreciate the play on words – "an excuse from living," instead of the more usual turn of phrase, "an excuse for living." Hickam was trying to say that medicine could become an overwhelming career, that it could completely consume a young doctor and prevent him from paying attention to other aspects of life. But the message only hit home later, Fred says, after his personal life had already suffered irrevocable damage.

The incident with the patient turned out to be a learning experience. True to Hickam's prediction, the man recovered; that same evening he devoured a full meal of potatoes without ever knowing that something potentially very dangerous had happened.

In 1969, as the conflict in Vietnam reached its height, Fred's career at the hospital was interrupted when he was called up into the U.S. Army. Fred was sent to California for a year where he was trained as a flight surgeon. During his time there he served as personal physician to General Omar Bradley, who had been deputy to Dwight D. Eisenhower and George Patton as the Allies invaded mainland Europe. In the 1960s, Bradley was one of a tight-knit group that advised President Johnson on the Vietnam War.

After that first year, Fred was put on a flight to Vietnam, where he expected to carry out a full tour treating helicopter pilots and their families. But he hadn't been in the country long before he was pulled out and sent back to California. "The military doesn't share their reasoning about these things," he says, "and I never knew the real reasons they brought me back. But I suspect it had something to do with General Bradley – he liked me."

When his service ended, he returned to the University of Indiana and his medical career took its course, albeit at a price. "My children were growing up, and I missed out on a lot of that," he says. "My marriage was a casualty as well – it was a predictable result of putting my career first, but one I noticed too late."

After the divorce, Fred decided he needed a new start, and the best opportunity might be a sabbatical. Physicians


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and academics are offered a year off, occasionally, to develop new skills and enlarge their horizons. It was 1983, and he began making plans to spend a year in Germany. He had visited relatives many times over the years, but he'd never spent a significant amount of time in his homeland. It would be a good change of scene.

But just a short time later, his life took a completely unexpected direction, for reasons that could ultimately be traced to events on the much grander scale of world politics.

My own arrival in Germany followed shortly after Fred's, just in time to witness the turbulent end of the Cold War. On November 9, 1989, my wife and I sat in front of our television in Heidelberg and watched the raucous events taking place in Berlin. The same scene was being replayed in nearly every living room in the country and elsewhere. At eight p.m. that evening, the German national news networks broadcast a press conference that had just taken place in East Germany.

Hungary had just been through a dramatic election that would deeply affect European politics. The new administration stated that it would no longer prosecute citizens trying to leave, so all along its border, people were throwing open fences (or cutting through them) and escaping to the West. Since East Germans could travel to Hungary with few restrictions, a surge of "vacationers" were making their exit along the leaky border. A friend of mine named Detlev Arendt, a developmental biologist who works in Heidelberg, used this route to smuggle his future wife and her two sisters into West Germany.

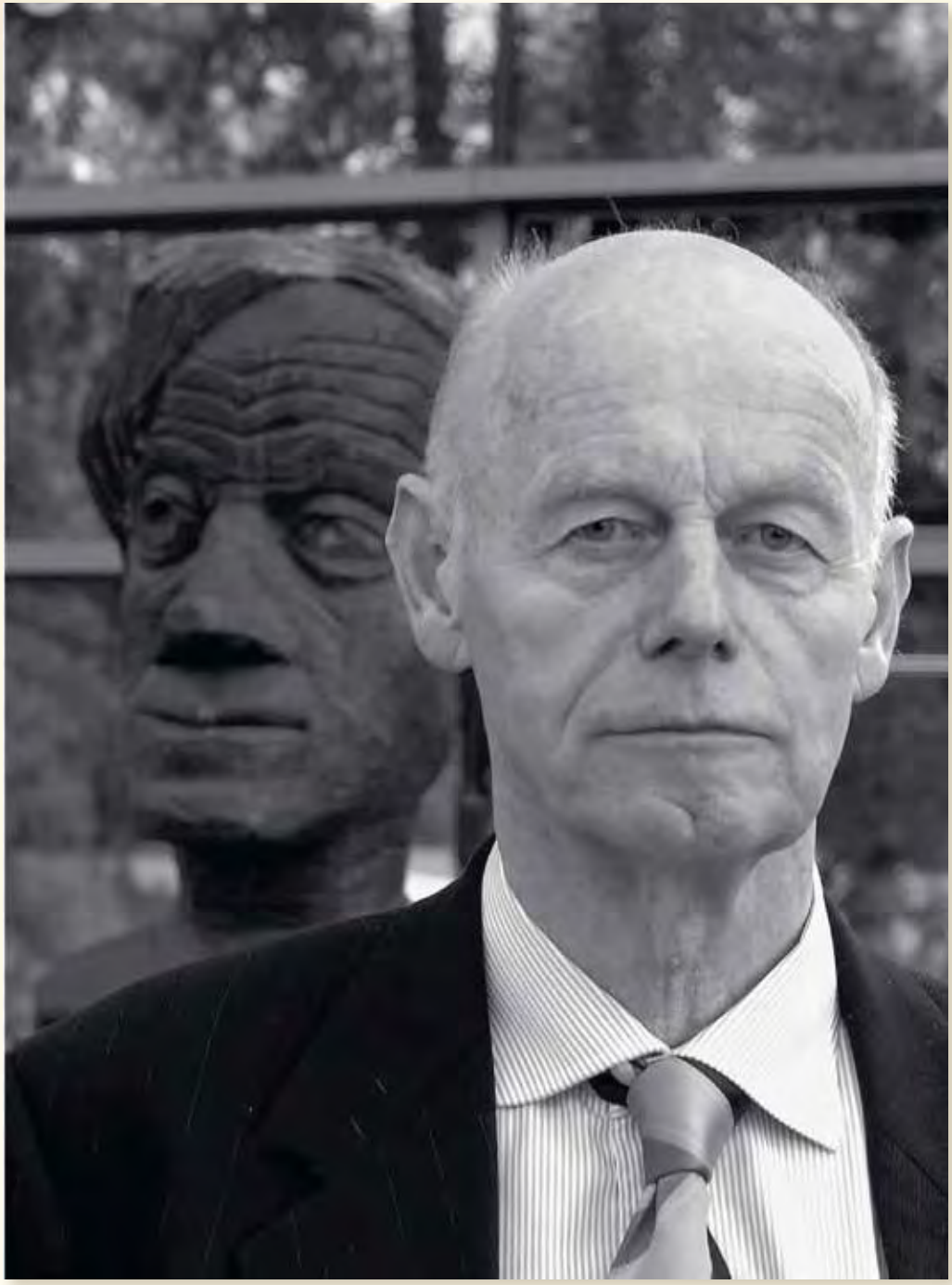
A few weeks of this triggered a shift in East German policy as well. Günter Schabowski, a spokesman for the East German Politburo, announced in a televised press conference that the German border would be opened. Deadly force would no longer be used to stop people who wanted to leave. The word spread quickly by word of mouth and through a West German television broadcast that could be watched in the East. Huge numbers of residents began amassing at the city's crossing points, in the middle of Berlin, and orders raced back and forth as border guards tried to decide how to behave. At 10:45, the confusion reached its peak, and the helpless guards threw open the gates. Crowds began surging through. There was no telling whether the situation would continue, or whether the border would once again be sealed.

It had taken years to build a Wall that had divided a city, a country, and a continent for a generation, but once a gap developed it began to crumble almost instantly. People clambered to the top and cheered and danced – just a day earlier, anyone who had tried to do so would probably have been shot. That had been standard procedure since 1961, when a tailor named Günter Litfin attempted to cross the border by swimming across the river dividing the city. He became the first of a long list of would-be escapees to be shot by East German guards.

A colleague who worked in Berlin in 1989 told me that on November 9 he came home from the lab, turned on the news, and immediately rousted his children from bed. They all headed downtown to take part in an unforgettable moment in history. People from all over the region surged into the city, many bringing along sledgehammers and chisels, attacking the ugly, concrete scar that had divided their country for 28 years. Most of them took home chips of the wall as souvenirs; all of them were intent on tearing it down.

You can still buy fragments of the wall in any gift shop in Berlin, complete with certificates of authenticity. The brightly colored ones come from the western side, where people could get close enough to apply graffiti.

The fall of the Berlin Wall had immense, personal consequences for nearly every German but particularly those



Detlev Ganten

in the East. Within a year, the western Federal Republic of Germany and its sister, the German Democratic Republic, would be politically reunited in a process that Germans now call *die Wende* – meaning a turn, or turning point. With the change came new rights for citizens of the East: They no longer needed a visa to leave the country. They were also finally free from the *Stasi*, or Ministry for State Security, which was dismantled after nearly four decades of spying on the inhabitants of its own country as well as foreign citizens and governments. By 1989 the Stasi had 91,000 official employees and a huge number of informants. People spied on their colleagues, their neighbors, and sometimes their spouses – all in the name of internal stability and security.

The positive changes of reunification were accompanied by others that weren't universally popular. Many citizens of the former GDR were rightly concerned about the devaluation of their currency and the potential loss of long-held jobs, pensions, and other benefits. Millions of people had spent their entire careers working within a system that placed a higher value on security than individual freedom; nearing retirement, many of them hankered for the security. For many, feelings of "Ostalgia" (the German word for "east" is "Ost") would linger a long time.

Reunification affected people in every walk of life, including scientists and other employees of research institutes in the GDR. The state system had supported tens of thousands of researchers, many on permanent contracts. They would now have to be integrated into a system that the new, unified government could afford and which operated under different standards: Federal and state-funded research had to be internationally competitive. Institutes and individuals competed for survival – and prestige – at home and abroad.

The German government commissioned panels of experts to examine the institutes and make recommendations about their future. On the list was the Central Institute for Molecular Biology, established by the GDR Academy of Sciences in the village of Berlin-Buch, on the northeastern side of the city.

The group assigned to Berlin-Buch included a 50-year-old scientist named Detlev Ganten, who held a professorship in molecular and clinical pharmacology in Heidelberg. His major field of expertise was the cardiovascular system, and his work had a particular focus on the causes of high blood pressure.

One of the people Detlev Ganten met during the evaluation of Berlin-Buch was Heinz Bielka, a former director at the Central Institute who has devoted his retirement to the scientific history of the campus. This began in the 1920s with the establishment of the Kaiser Wilhelm Institute for Brain Research on a tract of land originally intended for use as a cemetery. A chapel and a gardener's house had been constructed, and then the planners realized that the groundwater level was too high. The land had to be put to other uses. The close proximity of a hospital complex and an institute for the mentally insane suggested a scientific function. The authorities decided to build an institute devoted to brain science.

"Research has been practiced here under four political systems – the Weimar Republic, National Socialism, the GDR, and now the Federal Republic of Germany," Heinz says. "It would be a fantastic subject for a socio-historical study on the relationship between science and politics."

Heinz is a cheerful man with a quick smile and a shock of white hair that spills over his ears. He is now in his early eighties – although you'd never believe it – and still gives regular walking tours of the campus. His knowledge seems exhaustive and his energy inexhaustible as he strolls along the hospital buildings built in the early 20th century by the celebrated architect Ludwig Hoffmann.

"I first met Detlev Ganten when he arrived in Berlin-Buch after the fall of the Berlin Wall," Heinz says. "We were introduced when he served on the official commission that was considering the future of the Academy of Sciences. From the very beginning he made a strong impression. He had a difficult job – I don't think a better person could have been found to do it."

One of those jobs was to conduct an intensive analysis of the personnel and resources of the Central Institute. Upon its completion, Detlev and his colleagues came up with a unique proposal: to salvage its best characteristics and integrate some of its science and personnel into a new institute devoted to "molecular medicine." Named after Max Delbrück, the Center would have a mission that was truly visionary at the time: to translate findings from basic biological research into new forms of diagnosis, therapy, and prevention for major diseases affecting society. Cardiovascular disease would be a main focus, but the institute would also conduct research into cancer and neurodegenerative conditions such as Alzheimer's and Huntington's disease.

It was a bold move because of the cleft separating modern medicine – based on empirical research into patients, their illnesses, and treatments – and the new biology, whose focus was on the scale of cells and far below, at the level of single molecules and their interactions.

Within just a few years, this attempt to link basic and clinical research disease would prove extremely fruitful, particularly its broad focus on more than one type of disease. Time has shown, for example, that the disruption of common mechanisms in cells sometimes lead to cancer, cardiovascular syndromes, neurodegenerative diseases, or something else.

Creating a center for "molecular medicine" was a courageous decision made during turbulent times. "Hundreds of people who were working on campus were worried about their future and whether they would have a place in the new institute," Heinz says. "Professor Ganten impressed us because he immediately moved to Buch with his wife and a dog, invited us old-timers to the guest house, drank Flensburger beer with us, and proved to be an excellent listener. We quickly got the impression that he had earnest, honorable intentions and we could trust him."

Those were much-needed qualities as Detlev faced extraordinarily difficult decisions about who should stay and who should go. "He was willing to let the past be the past – if you could do your job well, he would do whatever he could to help you," Heinz says. "That went for the scientists and a lot of other people working on the campus, and for it to succeed he had to break a whole social system. Even though he was under a lot of pressure to make big, quick changes, he did the job fairly and with a deep psychological comprehension of what we were going through."

Among Detlev's qualities, Heinz says, was a love of the arts. "His effort to draw art and sculpture and other elements of culture together has had a deep and lasting impact on the campus."

Another long-term colleague of Detlev's, researcher Michael Bader, laughs about his experiences with the institute's first director. "He has an enormous talent for motivating people and persuading them to do things that they otherwise probably wouldn't have," Michael says. "Dozens of times I went into his office with an idea, or to argue about the way something should be done. I knew him a little by then and would go in determined not to change my mind. But every time I came out, I ended up doing exactly what he wanted me to do. I still don't understand this phenomenon," he laughs. "It was like some strange sort of 'mind control.'"

Detlev's talents at persuasion proved essential during the launch phase of the Max Delbrück Center. It was crucial to draw high-caliber scientists to the young institute. This was a daunting task because, given a choice, most researchers prefer to take on positions at well-established universities or research labs. Carrying out high-impact work was crucial to their careers, and that was most likely to happen in a community with solid infrastructures, where other groups were already thriving.

Among Detlev's first recruits was Fred Luft, who perfectly fit the profile of a physician with a deep interest in the molecular causes of disease. Successfully narrowing the considerable gap between laboratory and clinical science would require assembling an entire community of scientist-physicians with the right experience and mindset. Fred had another advantage: He was working, in general, on the cardiovascular system. Given Detlev's own interests, he wanted to build a strong cardiovascular program at the MDC.

Fred Luft and Detlev Ganten met for the first time in 1983. "I was preparing for my sabbatical year in Germany," Fred says, "and was on the road on my bicycle with a close friend, a clinical pharmacologist named George Aronoff. We had crossed the Alps on our ten-speeds and were cycling toward Frankfurt. We stopped off in Heidelberg and I presented myself to Detlev Ganten, who was working there at the time. He has always claimed that I had on one of those bicycle helmets with little rear-view mirrors attached by wires. I don't remember the helmet, but something good came of the meeting. Detlev suggested that I could spend a year with Thomas Unger, who was in the Department of Pharmacology at the University of Heidelberg at that time."

Fred began working with Unger's lab, boning up on basic biology while spending much of his free time cycling through the lush forests of the Odenwald – good exercise considering the 15-percent grades of many of the roads. He made friends among the medical students to whom he was giving lectures on topics in pharmacology, such as the treatment of tuberculosis. But establishing those friendships required overcoming a case of culture shock, which Fred recounts in his typical sardonic way.

"I was stunned because students came late to the lectures and they brought dogs along with them," he says. "Then there were constant 'clicking' noises in the background. I had no idea what they were – as it turned out, apparently, the young women came to knit and the guys played with their dogs."

Detlev and his wife Ursula, an investigator in her own right, invited Fred into their social circle and the two men spent hours talking about health problems related to hypertension. One of their many collaborations involved an international investigation into the relationship between a person's salt intake and blood pressure.

"The study investigated salt intake in the general population and its relation to hypertension," Fred says. "Salt is generally portrayed as the criminal in most people's hypertension; our study showed that the relationship is 'weaker' than many people had assumed. Well, there's still a controversy about this, and I'm still caught up in it. Aside from everything else we're doing in the lab, it's another story that we're working on right now."

The issue is that salt intake and excretion are invariably coupled to blood pressure, presumably through an increase in the volume of fluid in the body. "All of us experience changes in our weight and well-being on a daily basis, partly as a result of the salt and fluids in our diet," Fred says. "Normally those alterations stay within an acceptable range. But if a person experiences hypertension over a long period of time, they are said to suffer from *essential hypertension*.

It's a misleading term, Fred says, but appropriate at the time it was coined – because early clinicians thought people "needed to have it." The dangers of high blood pressure hadn't yet been recognized; physicians observed it in many patients, but didn't realize that lowering it could have significant health benefits. It often occurred in people with damage to blood vessels in the kidneys, suggesting that the problem was mechanical: forcing blood through damaged arteries would require more pressure.

In non-essential hypertension, this perspective makes sense. If you think of the vasculature as a closed system, like a garden hose attached to a faucet at one end and sealed off at the other, it's easy to see how the amount of fluid can raise blood pressure. Just let more water enter the hose and try to pinch it. If the pressure is high, and you pinch it over and over, you're going to build up muscle in your fingers and hand. The same thing happens to the heart as it tries to pump fluid through the system, which is why people with long-term hypertension usually develop an enlargement of the chamber of the heart responsible for pumping.

"Franz Volhard, the cardiovascular pioneer in Berlin, was one of the first people to realize that you ought to lower blood pressure," Fred Luft says. "He wouldn't have called it essential – he called it dangerous." But the name was out there, and it stuck.

During his sabbatical in Heidelberg – which ended up stretching almost three years – Fred met his future wife, Ursula. "She wasn't the only reason I decided to permanently move to Germany in 1989," he says, "but she was surely no hindrance." When Detlev moved to Berlin in 1991, one of his first decisions was to offer a job to his former colleague. By that time Fred had moved to a position in Erlangen.

The stint in Erlangen led to another chance encounter that would later play an important role in the study of the Turkish family. When Fred arrived, he found a young resident named Ramin Naraghi on the staff. Ramin, too, was interested in hypertension, but from the point of view of a surgeon.

I met Ramin in his tidy apartment in Ulm, perched on the edge of the city, with a balcony that looks out over a farmer's vast green fields. They don't grow black tea in Ulm, but Ramin says the view calls to mind the plantations that he saw in Turkey, and it motivated his choice of the apartment. His trips to the Black Sea Coast now lie more than 15 years in the past, but they marked him as well, and the memories are as close as a glance out the window.

Ramin is now fifty years old – you wouldn't guess it but for the grey that has crept into his black hair, because he talks with the enthusiasm of an eternal student. Maybe it comes from some abrupt and dramatic changes of culture that he experienced at critical junctures in his life. His father is Austrian, his mother Iranian; when he was six years old she moved with him to Teheran, where he lived until he was 14. In the years before the revolution, the city was a blooming, prosperous mixture of Western and traditional influences.

"I attended a German school there, but the time in Persia and the encounter with its culture really had a formative influence on me," he says. In 1976 he returned to Germany and went to school in Bonn. School helped nurture his immense curiosity. He has never shied away from new ideas, even unusual ones that go against the grain of academic tradition.

In school he liked science, particularly physics, and was also interested in mechanical engineering, but as he sat down to choose a major at the university these fields suddenly seemed dry. Medicine was an impulsive choices. "I was sitting around with two friends who were deter-

mined to study medicine – their parents were doctors, and becoming a physician was their whole goal in life," he says. "I thought, 'Why not apply?', and we made a bet about who would get accepted. I was the one who got in," he laughs. "They were upset about it."

In medical school he was surrounded by students determined to succeed. "A lot of them found the first degree stressful," Ramin says. "The main subjects were biochemistry, physics, chemistry, and physiology. Most of this wouldn't directly impinge on a medical career, and students with a fixed image of their future profession tended to neglect these subjects. More and more got frustrated as the years went along. For me, it was the other way around. There were so many interesting topics in these courses, and I could look at them in a fresh way and pursue those that really interested me."

He became interested in neuroanatomy, he says, because of the "mathematical" construction of the brain. "This organ and its parts have logical functions and are connected to each other in a logical way. And in surgery you're in direct contact with the 'object'. I'm a manually-inclined person who likes to build things and solve problems manually, which is an ideal combination for neurosurgery."

In Hannover Ramin had the opportunity to observe a controversial bit of surgery that changed his life.

"Medicine is very conventional," he says. "There is a political and social system and a particular style of doing things. Personalities play an important role. If you ask a question, or call an accepted method of doing things into question, the physicians who have been doing things the 'old way' often feel like they're being personally attacked."

The operation he witnessed was the result of a radical idea that stretched back to 1967. That year the American physician Peter Jannetta, a neurosurgeon in Pittsburgh, Pennsylvania, discovered something that would change

the way many doctors thought about the connection between blood vessels and nerves.

"As a young intern, Jannetta had made some neuroanatomical preparations, and during this time he observed something striking in one of the sections," Ramin says. "He noticed that a blood vessel lay directly on a brain nerve, and the section had come from a person suffering from a severe form of facial pain called *trigeminal neuralgia*. It's a terribly painful syndrome – imagine your worst toothache times 20 or 30."

This single observation set the course for Jannetta's entire career. Somehow, he believed, a blood vessel compressing a nerve could result in terrible pain. A short while later he managed to perform surgery on a patient suffering facial neuralgia. The intervention involved displacing the blood vessel by moving it away from the nerve and separating them by a padding. After the procedure, the patient was completely free of pain. Repeating the operation on more patients with neuralgia, facial tics, and other neurological conditions brought success after suc-

Ramin Naraghi

cess. Jannetta began attending conferences to report on the cases.

"Suddenly there was a successful treatment for a condition that had evaded all other approaches," Ramin says. "It was based on a completely new hypothesis about the cause of these syndromes. Jannetta quickly became one of the most famous neurosurgeons in the world. At the same time, all this was very controversial – a lot of people found the concept exciting, but he was attacked because so many others didn't want to accept it."

The operation became known as the Jannetta procedure, or microvascular decompression, and Ramin witnessed it in Hannover. The subject was one of Ramin's own patients in the hospital where he worked as an intern, a man with a severe facial spasm. The patient agreed to undergo the procedure. It was carried out by Madjid Samii, a well-known neurosurgeon who now heads the Neurosurgical Center in Hannover. Samii opened the brain behind the ear, found the blood vessel compressing the nerve, and pulled it carefully away. A padding made of teflon was inserted to keep them separate.

"After the surgery, the facial spasm was gone," Ramin says. "And there was another very interesting effect. Prior to the operation, the patient had high blood pressure. As I checked in on him afterwards, day-to-day, I noticed that the blood pressure was going down. It went down so far, in fact, that the patient no longer needed to take medicine for hypertension."

Intrigued by the connection, Ramin began devoting his spare hours to searches of medical literature in the library. It was an arduous task. Articles were summarized as abstracts and indexed by keywords in a printed publication called the *Index Medicus*. Researching the connection between hypertension and blood vessels required pulling down volume after volume, and tracking down articles with relevant keywords.

Night after night of these efforts were finally rewarded. Jannetta had also noticed the effects of the surgery on hypertension and described it in a small number of patients. "This link was another very controversial idea," Ramin says. "Nobody really took it very seriously. Making the case would require a much more extensive study. But there was a clear way to proceed: to look at patients with high blood pressure and try to detect the presence of a blood vessel compressing a nerve."

Jannetta pioneered another way of testing the hypothesis by artificially inducing hypertension in baboons. He inserted a thin tube into their brains and inflated it until it put pressure on the nerve. Over and over, this caused a rise in blood pressure. Once again, this wasn't definitive proof, but the case was getting stronger.

Ramin's next stop was the pathology department of the Hannover hospital, where autopsies were routinely performed on deceased patients. "Jannetta's operations focused on a structure in the brainstem called the medulla oblongata," he says. "Studies of human patients and laboratory animals had demonstrated conclusively that this part of the brain plays an important role in blood pressure. It controls the parasympathetic nervous system – regulating involuntary processes in the body.

"A lesion or an injury to this area often causes a patient to experience a huge drop in blood pressure," Ramin says. "Physicians had refined the experiments by stimulating the area with electricity and drugs. So we knew that this region was very deeply involved in blood pressure regulation. Thus it was reasonable to think that if a blood vessel passed by there, there might be a connection."

Ramin decided to carry out a thorough investigation of the brains of patients who had suffered from essential hypertension. The hypothesis predicted that they ought to have a loop of blood vessels in this area pinching a nerve

that wouldn't be found in those with normal blood pressure. Ramin decided to make the topic the subject of his doctoral thesis. He came early in the morning and late at night, borrowed a microscope, and carried it down the long walkway connecting the laboratory to the pathology department. Whenever there was an autopsy going on, he peered directly into the exposed brain and documented what he found.

Time and time again, he found that patients with essential hypertension had a particular loop of a blood vessel along their medulla oblongata, lying directly alongside a nerve. It lay half a centimeter below the other nerve that Jannetta had made famous, the one that could cause people to experience extreme pain or facial tics.

So far all of this work had been carried out on the deceased. When Ramin moved to Erlangen, Ramin began considering ways to study the vasculature of living patients. The only reasonable technology to do so was *magnetic resonance imaging*, or MRI, which had been used to peer into bodies for about twenty years. Some of the best MRI instruments were being built by the company Siemens right in the city of Erlangen. As a result, the University Hospital was being used as a proving ground for the latest, most advanced machines.

"Starting at that point," Ramin says, "I began spending my nights in the MRI lab, trying to find a technical solution to visualize the relationship between nerves and blood vessels. Every generation of machine got better – today it's easy to do this. A side effect was to allow me to try, using this technology, to observe patients with hypertension and study whether they had this displaced nerve or not."

MRI technology is based on the production of a magnetic field so strong that it reaches into the nuclei of atoms and causes them to realign their own magnetic fields. Water is built of oxygen and two hydrogen atoms; the nucleus of each hydrogen has one proton, and the two spin

around each other. The magnet changes their spin – imagine bringing a big magnet up to a table full of compasses, and pulling all their needles away from North. When the magnetic field is relaxed, the spin of the protons snaps back to their normal position. This emits a radio wave that can be detected by the machine. The data is assembled into an image in which areas of high and lower water content appear in sharp contrast.

Various types of atoms are affected in different ways. By tuning the machine in different ways – using different *sequences* – the machine can highlight different structures in the body. One MRI sequence could be used to detect blood vessels, and another to highlight nerves. By combining the two images, Ramin could relate the positions of vessels and nerves.

In Erlangen he had the technology, but needed patients. One day he attended a conference in the Intensive Care Unit and met a new colleague from the Nephrology Department – Fred Luft.

"I don't remember exactly what case we were talking about that day," Ramin says, "but I was struck by the very open way he discussed the problem with us. I was just a

young doctor, and here was this very experienced physician, but I was expressed by the open, analytical way he approached the problem. There was none of the egotism you so often find among high-ranking physicians. He was focused on finding a solution."

Approaching a senior colleague with a controversial idea was always a challenge. "People sometimes take the attitude, 'Okay, here's another nut, what does he want?'" Ramin says. "But I took the chance. I visited him a few days later and laid out the whole concept of microvascular compression. I explained Jannetta's concept and told him I'd followed it up on deceased patients, done my doctoral work on it, and now had access to state-of-the-art MRI machines."

He explained that the principle had been established in the case of trigeminal spasms, and now various surgeons were wondering whether it might play a role in other conditions. The real coup, he said, would be to find a strong correlation between a pinched nerve and hypertension in living patients.

"The idea clicked," Fred says. "The rostral vetro-lateral medulla, which is the area of the brain that Ramin had focused on, is critical for blood pressure regulation because it is the most important switching station for the sympathetic nervous system. Ramin and I agreed that somebody ought to try to figure this out."

"Professor Luft immediately agreed to help," Ramin says. "We wrote a proposal for the ethics commission, which was accepted, and then he motivated all of his colleagues to participate. He found collaborators and within the shortest possible time we had begun the study. The goal was to compare hypertensive patients with normal ones, and then with patients with other forms of 'secondary' hypertension. To do that we had to demonstrate the relationship between the brainstem and blood vessels and find a significant difference between these types of patients. The results were very positive and led to a publication in the *Lancet*. It was wonderful for my career – you have to consider that I'd just graduated from the university, and this was a very important accomplishment."

The work produced not only a publication in the *Lancet*, but also generated an atmosphere in which everyone in the project was highly motivated, pulling together to gather evidence for an unconventional hypothesis. Things were running smoothly when, in 1992, Fred Luft announced he was moving to Berlin-Buch.

"That's that," Ramin thought. "We were able to continue working with the team, with the people who remained in Erlangen, and we could even extend it to a surgical study. But a key player was gone and would be sorely missed."

Ramin didn't anticipate that Fred would continue turning the results of the project over and over in his mind. Or that within a few years, he would get a call from Fred in Berlin, asking whether he wanted to continue his work on a very unusual family.

8 A meeting of minds

Berlin-Buch was in a state of disarray when Fred Luft arrived, half-university campus in character, half-construction site as renovations were carried out on existing laboratories and ground was broken for a new building. Fresh arrivals like Fred were being housed in the old GDR guest houses, and to move between buildings you took the small paths through a wooded area.

This patch still exists. Walkers encounter some of the sculptures commissioned for the campus through an initiative by Detlev Ganten, drawing on funds from the national German Lottery. Many are particularly poignant: Anna Franziska Schwarzbach crafted a sculpture of a child with closed eyes and an upturned head that emerges from a twisted, fragmented body – a memorial to the children that had fallen victim to the Nazi regime. During the Holocaust, scientists on the Berlin-Buch campus had examined brain tissues from some of the victims. It was a severe violation of medical ethics which, the campus founders felt, should never be forgotten. The sculpture is a daily reminder that many of us pass by on the way to work.

What really attracted Fred to the campus was Detlev Ganten's vision of unifying basic and clinical research and the possibility of setting up a new kind of research program to

bridge the gap. Over the past few decades, molecular biology had made huge strides toward identifying genes responsible for disease. Maybe it was time to turn that knowledge – and the technology that made it possible – to syndromes that had long resisted an explanation. Maybe it would finally be possible to trace conditions such as cardiovascular diseases to their genetic causes.

"And finally," Fred says, "it wasn't such a bad place to ride a bike!"

Between 1992 and 1993, a unique group of researchers and doctors began assembling around the figures of Detlev Ganten and Fred Luft on the Berlin-Buch campus. Many of them gave up promising careers at other prestigious laboratories in order to participate in the "experiment" of a new institute with a new vision.

One of those scientists, Herbert Schuster, is now a private physician with his own practice in Berlin, where he offers services in genetic counseling. I first met Herbert one evening in his spacious office with high, ornate ceilings, in the city center. Despite the fact that he'd just been through a long day of consultations with patients, he was eager to talk about one of the most exciting phases in his life.

In the early 1990s he was a young physician with a rewarding, tenured research position at the University of Munich. "I had a fabulous mentor," he says. "Nepomuk Zöllner was a biochemist with an extraordinary enthusiasm for the tiniest details of biochemistry. He simply wanted to know everything that could be known. And he transmitted that enthusiasm to his students."

Zöllner was an expert on the way the body metabolizes cholesterol. Years of public health campaigns have made most of us aware of its role in cardiovascular disease – high levels of certain types of cholesterol clog and damage arteries, raising blood pressure and causing other problems.

But it plays an important role in many processes in our cells: first as a crucial substance in cell membranes, and secondly as a molecule that is whittled down to make steroid hormones, acids, and vitamin D.

Zöllner's international reputation gave him a seat on the evaluation commission as the German government began considering the fate of former Eastern scientific institutes and universities. His main responsibility was to look at the activities of the University of Dresden, with a tradition of research into cholesterol and high blood pressure. Zöllner's response to the invitation was to say, "Of course I can take part, but why don't you take one of my very competent young people instead?" He put forward Herbert Schuster's name. "Herbert is familiar with the technologies, and he has a good idea of what might be possible in the next ten years."

Detlev Ganten was in charge of the team in the area of hypertension, and soon after the group began its work, he assumed the directorship of the MDC. Herbert had heard of the new institute and was curious. "I wondered what they had in mind," he said. "So one evening during the evaluations, when we had some time, I asked him to tell me about the new place. He took the opportunity to ask about my own biography and learned that I had a broad background in internal medicine and was deeply interested in metabolism and genetics."

"You should come visit us in Berlin," Detlev said. Herbert got away for a few days in October, 1992, and witnessed some of the first steps in the development of the new institute. A few months later, when the committee met again, Detlev said, "You must come again; you'll be amazed at what's happening."

Herbert Schuster

Fred Luft was already there, setting up a program to carry out work in molecular genetics. "It was something I knew practically nothing about," he says. "I could spell genetics, but that was about it. For example, I knew that in German it ended in a 'k', and English with an 's'."

In fact, he had already gotten his feet wet – "Well, put one toe in" – in a human genetics protect involving twins in the United States. "The National Institutes of Health had recruited an amazing number of twins for a huge study – something like 20,000 pairs of twins," he says. "But my encounter with that project was virtually everything I knew about it.

"Then in 1992 I was in Berlin, and was sitting in some hole of an office facing a mountain of applications. The position hadn't even been advertised yet, but people had already been applying for all sorts of things. I was supposed to look for someone who had clinical training and some sort of interest in molecular genetics. At that point we weren't really concerned about a specific topic, we just needed to find people who would fit. I came across Herbert's CV and threw it onto the pile of possibles to the right, rather than the pile of impossibles on the left, which was already way too high."

So Herbert came for a second visit. For one of the labs, he gave a talk about his research into the genetics of cholesterol metabolism in humans. The group had been carried over from the GDR Central Institute and was run by Michael Strauss. In attendance was a young PhD student named Sylvia Bähring, who was trying to figure out what to do after finishing her PhD. He didn't know her at the time, but that would soon change.

The second memorable event of that trip was his encounter with Fred Luft, and that meeting would be life-changing. "I have to admit I was afraid to leave a very well-established research environment," Herbert says. "It was a sharp contrast to Buch at that time which was, well, basically a construction site. Everything was grey, there was no color at all. But within just a few minutes of meeting Fred Luft, I had the feeling again – this was someone I could learn a lot from, someone who would really take care of his students and colleagues. The feeling was so strong that I was willing to give up the security of my old position."

In March 1993 he arrived for a week, a sort of mutual test. "Fred was sitting in the old 'Gatehouse' of the campus, with most of his stuff in boxes, not yet unpacked. He was living in the old guest house from GDR times. All of this seemed both quite primitive and a great adventure."

During that first week, Herbert says, Fred invested an unbelievable amount of time in making him feel at home and engaging him in wide-ranging discussions about science. "He still had a house in Wiesbaden, and was commuting on the weekends; during the week we were all basically living together on campus. We made plans, sketched out ideas, and talked and talked. The goal was to find an intelligent way to structure our work. This fantastic vision of molecular medicine had to be made concrete in the form of specific projects and experiments."

In Berlin he would be able to do anything he wanted. As a clinical geneticist, he would be able to do field work, talk directly to patients, working out pedigrees and following up on their health. Munich had been satisfying, he says – he cut his teeth as a researcher there – but in Berlin the attitude was, "What do you want to do? What will it cost?" If you could break things down that way, they said, "All right, let's do it!"

"Fred simply hungers for knowledge," Herbert says. "That motivated him to seek a much deeper understanding of health and disease than was available to either scientists or physicians. It was child-like, in a way, the way a child has limitless curiosity, but in Fred this was combined with an extraordinary amount of know-how." The result was an incredibly motivating environment. "We all

Hakan Toka

would have worked ourselves to the death for him, for this project."

When Herbert made the move to Berlin, he brought along a young, tremendously talented medical student named Hakan Toka. Hakan had been born in Germany to Turkish parents – part of the wave of foreign workers. It was another relationship that had come about by absolute chance, but one that would turn out to be absolutely crucial in starting up a project to follow Bilginturan's initial study.

Herbert needed staff to fill out his new research group in Berlin: postdoctoral fellows, PhD students, and technicians. One of his early recruits was Sylvia Bähring. She had grown up in East Germany and completed her undergraduate studies at the Central Institute for Molecular Biology; then the campus was reformed during German reunification. She was initially accepted into the lab of Sinaida Rosenthal, a biochemist and geneticist, to work on her PhD. But within just a few months, cancer claimed Rosenthal's life. Sylvia switched to the group of Michael Strauss.

Finishing her PhD brought the title of "Dr," and the need to consider the next stages of her career. Sylvia continued working in Strauss' group as she thought about what sort of laboratory she would like to join. Normally, biologists with a PhD do one or two stints as a postdoc in new labs, the more prestigious the better, gaining independence and experience and carrying out their own projects with the ultimate aim of running an independent laboratory. So the best thing to do would be to move, but where?

Sylvia had met Herbert in 1993, when he had given a talk to the Strauss group about his research on cholesterol, involving sequencing the DNA of patients afflicted by genetic diseases. The lecture struck a chord; Sylvia decided it was the type of work she wanted to do. Within just a few months, Herbert had joined the staff of the MDC. Sylvia sent him an application, went through an interview, and was quickly accepted into the new lab in April 1994.

The MDC was growing quickly and needed to find space for Herbert's group. A solution was found in the basement of the Franz-Volhard Clinic, on the other side of the village of Berlin-Buch, where offices were cleared to create laboratory space. Since the rooms hadn't been planned as labs, things were cramped – one of the scientists who worked there told me it was like doing molecular biology in a submarine. Or a pressure cooker. Scientists worked practically on top of each other, and it didn't take long to get to know your colleagues and their quirks.

"One of the problems was that the rooms weren't high enough to install some of the equipment and the ventilation that was needed," Fred says. "At that point it was either raise the whole building somehow, or lower the floors, so they ended up tearing out the floors. Herbert and everybody else just had to wait until they finished."

Those labs would be used for about 15 more years, until the vast tract of land in Berlin-Buch where the clinic was located would be shut down, and the Volhard Clinic moved out of its cozy brick building. It was a shame to abandon this splendid second campus, a spacious area replete with beautifully sculpted fountains and ornamental pavilions, with paved walkways that stretched between clinics. The buildings that housed them were equally beautiful but bore the signs of neglect: broken windows and fractures in their ornate tiled floors, with scars marring the ornate woodwork. Modernizing the clinics – while respecting stringent rules of historical preservation – would have cost a fortune.

Herbert's plan to search for genes related to disease would require extensive technology. His lab in Munich had bought equipment from the company Applied Biosys-

Thomas Wienker

tems (ABI). When he announced that he would move to Berlin, the representative from Munich alerted his counterpart there and told him to greet the group and make sure they were happy with the products.

"Their technology had been instrumental in our cholesterol research, and I told them that," Herbert says. "When I arrived in Berlin, we had funding to set up a superbly outfitted laboratory, most of which came from Applied Biosystems: sequencers, pipetting robots, and other tools we'd need." He found his technician in Atakan Aydin – another German-born scientist of Turkish heritage. Although none of them knew at that point they'd be working on a project involving Turkey, the recipe was perfect when the occasion arose.

"All of this was, for someone who was actually a physician, an unbelievable opportunity," Herbert says. "I was going to get to work with talented scientists like Fred Luft and Sylvia Bähring and establish a mixed laboratory which combined clinical with basic research, medicine and biology." He laughs. "In a short time, we'd come a long, long ways from those boxes in the Gatehouse."

Like most of his colleagues at the new institute, Herbert was chomping at the bit to start pushing medicine into a new era. "We had been coping with symptoms," he says. "Now we wanted to move toward early diagnosis and prevention. Our goals were to understand how diseases function, to develop strategies that could shorten the phase of an illness, or prevent disease from developing in the first place."

Herbert likens the era to a historical parallel. "You might compare it to what happened during the Renaissance, when physicians suddenly discovered anatomy," he says. "This caused a huge shift from the earlier view of humans, which had predominantly been spiritual. During that era, the close study of organs suddenly cast medicine into disarray. A lot of people ended up losing their heads – and I don't mean that metaphorically."

The last established scientist to join the group on the Berlin-Buch campus turned out to hold the key to starting the Turkish project. Once again, it was an arrival that happened largely by a series of odd coincidences. Without a crucial discovery by Thomas Wienker, Fred and his colleagues might never have become aware of the family that would occupy so much of their efforts in the coming years.

I met Thomas in his office in the Max Planck Institute for Human Genetics in the south of Berlin, the other extreme of the city, by chance on his birthday. A colleague had just delivered an extravagant bouquet of flowers that sat behind him on the windowsill as we talked. The whole time it seemed to hover over his shoulder.

Thomas Wienker had received his *Habilitation* – the prerequisite to a professorship in the German academic system – far to the south, in the charming old city of Freiburg. "It wasn't the easiest topic to pursue because it was an 'outsider area,' at the intersection between mathematics and genetics," Thomas says. Karl Sperling of the Free University of Berlin, whom Thomas calls an "elder statesman of genetics," was impressed by Thomas' work and invited him to give him a talk in Berlin.

Sperling's accomplishments merit a book of their own – alongside the volumes he has written himself. In 1984, long before the arrival of technology had made the dream of a Human Genome project remotely feasible, Sperling gave a talk entitled, "The molecular analysis of the human genome – new insights, threatening perspectives?" Anecdotally, alongside his many studies of genetic aberrations and their influence on human health, he helped carry out a study in the aftermath of the nuclear disaster in Chernobyl. The goal was to establish whether a radioactive cloud that passed over Berlin might have been responsible for a sudden rise in cases of Down syndrome births that occurred nine months later.

As well as having been a pioneer in human genetics, Sperling has played a crucial role in fostering the career of many young scientists and helping create new institutes, such as the MDC. One morning in the early 1990s, at seven a.m. he met with Detlev Ganten – typical working hours for Detlev – to encourage the creation of a "microsatellite center" at the new Max Delbrück Center. He was referring to the core technology that Herbert Schuster, Fred Luft, and their colleagues would soon require.

Over the years, Fred emphasizes, Karl Sperling has been continually helpful in supporting the project. "Why should anyone believe that a bunch of crazy clinicians could come up with something?" Fred says. "Yet all those years, despite a lot of negative results, he's one of the people who have kept the faith."

This was the context when Sperling invited Thomas Wienker to give a talk at another institute in Berlin in 1993. "He wanted me to prepare something on hypertension," Thomas says. "It was a bit strange; Sperling had never worked on that. But I was to address the question of human genetics as applied to high blood pressure."

After his talk, Sperling told him, "Thomas, I'm sorry I don't have much time to talk because I have to go to the MDC and referee a bigger project that's being considered by the German ministry. Why don't you come along? Your theme is important; maybe you can help."

"So I went along for my first visit to Berlin-Buch," Thomas says. "There on the spot it was quickly arranged that I give a talk about my work. Detlev Ganten was there, and Fred Luft, and Herbert Schuster, and several other people. As it turned out, they were considering a huge project, worth four and a half million D-marks."

Thomas delivered his presentation, left the room, and then was called back in as an expert on human genetics. Fred Luft told him, "You know that hypertension is at stake here. What would you do? If you were sitting here, what would you do?"

"Well," Thomas says, "I was ready for this. I don't know whether this had happened by accident or design on the part of Sperling. I suspect the latter – it was precisely the topic that he'd had me prepare."

That had been a major chore. By 1993 the Internet was in its infancy and Thomas made a search using a text-based tool called Gopher, which crawled through documents on servers and looked for keywords. But there was very little content on genetics. "So for several nights I sat in the library of the Institute of Genetics in Freiburg, going through all of the volumes of *Excerpta Medica*. There were literally meters of books on the shelves that had to be skimmed for abstracts on hypertension."

On one of those nights, he came across a startling abstract by a Turkish physician named Nihat Bilginturan. The paper described a monogenic disease that caused astronomically high levels of hypertension among an extended family of farmers on the coast of the Black Sea.

"I'll never forget the moment I saw that paper," Thomas says. "It was absolutely electrifying. Here was this wonderful study that had been sitting there for two decades, published in the *Journal of Medical Genetics*, and nobody had considered it. I thought, 'The time has come to work on this. We can use positional cloning to find the gene.'

"So now in Berlin-Buch, in the referee round, I pulled out the copy I had made of this paper and said, 'This should be worked on.' And I can see it before my eyes, just the way it happened – Fred Luft made a note."

Thomas was immediately taken by Fred's "flamboyant character." "He was brilliant, very charming, and called to my mind a famous statement in science by the Nobel Prize-winner Werner Heisenberg. *'Wissenschaft wird von Menschen gemacht' – 'Science is made by men'.* That is Fred Luft. He has a brilliant ability to penetrate complex

topics and bring them directly to the point. Have you read his editorials in the *Journal of Molecular Medicine*? Small marvels, not only from the scientific point of view, but in terms of language and a philosophical perspective…"

He enjoyed how Fred's acuity often slipped over into a sort of irony and sarcasm that was expressed, Thomas says, "at the highest level of language." And how Fred often turned it on the simple day-to-day challenges that could arise daily, at any moment, under the difficulty of developing new infrastructures in the former Eastern states.

"A lot of small, practical things were very difficult," Thomas says. "Just trying to get a telephone was a nearly impossible task. 'Oh, to get a number… You'll have to wait about a year,' they told me."

But the MDC had the magnetic personalities of Detlev Ganten and Fred Luft going for it, and Thomas says that Detlev seemed absolutely indefatigable. "Sometimes late in the evening, I'd be working in the lab at 10pm or so, and there would be a knock at the door. You'd open it and Detlev Ganten would be standing there. He'd say, 'I was just passing by, I just wanted to say hello. How's it going? Are you having any problems?' You would chat for ten minutes and then he would move on to the next room."

You could approach the director at any time. "If the light is on," Detlev said, "the door is open." His secretary, would be there as well, often until 11pm for days on end. "I'd knock at the door and she would say, 'He's just on the phone, could you wait a few minutes?' And as soon as he finished, you could go in.

"Sometimes I would go there because I had become depressed, and he would tell me, 'Dr. Wienker, a person must never allow himself to be pulled down by external circumstances. If things are going well, that's good, but if they aren't, you can't let them influence you.'" Thomas had come in thinking, "This can't go on; I give up!" but he always left thinking, "I can do it!" He, too, had fallen subject to Detlev's peculiar form of mind control.

He remembers another of Detlev's sayings: "Das Geld liegt auf der Strasse!" Loosely translated: Money is just lying around on the street, waiting to be picked up.

In other words, any decent researcher ought to be able to find funding for his projects – providing he is willing to write grants, and preferably lots of them.

The fact that Detlev Ganten and Fred Luft were building houses in Berlin-Buch impressed the colleagues from the former Central Institute; most new staff members had chosen to live in more luxurious areas of the former Western sector in the city center. The men were trying to convince their colleagues that Buch was habitable, that it would grow and develop infrastructure.

Building a house in the East was hard, especially in the early 1990s, and trying to do so in Berlin-Buch could bring you to the edge of a nervous breakdown. The process, Thomas says, brought Fred to new heights of caustic irony. The work was going slow. The builders had to contend with the same high groundwater that had changed the fate of the campus from cemetery to research center.

To make space for the foundations and basement, you had to dig a hole. The bulldozer inched forward; it immediately filled with water. "They keep calling it my home," Fred exclaimed. "What it is, is a pit in the Earth, and it's full of water. I ought to turn into a tadpole or something."

Thomas remembers how Fred described the route to the campus to a visitor in those early years: "You go far to the northeast of Berlin. You leave the city and then there is nothing. Kilometer after kilometer of 'Hobrechtfelder'." Referring to James Hobrecht, the person who had designed the entire sewage system of Berlin, and channeled it to the empty regions to the northeast. "Kilometers of sewage," Fred said. "If you flush something in the city center, well, you'll pass it on your way north.

Atakan Aydin

Unless," he remarked sarcastically, "it landed in the pit of my house. If you finally escape that, you're greeted by some old houses built in that wonderfully aesthetic GDR style, and then you get to campus."

Thomas Wienker was soon hired by the MDC to join the laboratory of Jens Reich. The lab had been carried over from the Central Institute because of the importance of its work in the field of bioinformatics – the use of computers to study DNA sequences, genetics, and any other biological problem that could benefit from the use of statistics and mathematical modeling. It took Thomas a while to fit in, not only for scientific reasons.

"I was born in 1945," Thomas says, "so when you think of the generation of 1968, think of me. I was determinedly leftist, had a history of that, and never denied it. That was a shock for some of the other members of the group. If my political tendencies had been to the right, everyone probably would have known how to deal with it, but leftists aroused suspicion."

At ten a.m. in the morning the group often took a break and would discuss "everything in the world. Sometimes," Thomas says, "we would start by thinking about some biological problem, move to politics, and end up with Thomas Aquinas."

Those who know Jens Reich, who also merits a book of his own, won't find the range of topics surprising. Alongside a fascinating career in research – he holds two doctorates and has long been a pioneer in the mathematical modeling of biological systems – Jens has maintained a lifelong interest in philosophy, history, politics and culture and regularly gives "science and society" talks to the general public. As a citizen of the GDR he became active in citizens' rights issues, helping found a group called the "Friday Circle." Its membership comprised about thirty critical thinkers and their discussions usually centered around political and social reform. This brought them to the attention of the Ministry for State Security.

When the Stasi's files were opened in the wake of German reunification, Jens was not surprised to find an extensive record of his activities. He was a little more surprised, he says, to find photographs of his living room, of himself, his wife and their guests, taken from the attic of a building across the street.

In 1994 his name was put forward as an independent candidate for President of Germany, a largely symbolic gesture for a largely symbolic position. He wasn't appointed, but a few years later the federal cabinet named Jens to the National Ethics Commission. When the group was reformed into the German Ethical Commission in 2008, he was appointed again.

So it is little wonder that when Thomas Wienker joined the lab in 1994, he found himself in an environment where discussions could range from the microcosmos to political and social issues. Adding a confirmed leftist to the group was like bringing a new spice into the kitchen. But Jens says that Thomas settled in well: He proved to be an excellent teacher, and carried out his research work with an almost maddening precision.

Thomas' political tendencies might have put him at odds with Fred Luft. "In 1968 I was demonstrating against Vietnam. He was *there*," Thomas says.

But Fred hadn't wanted to be: like most of his intern classmates, he had applied to the NIH for a fellowship to avoid the draft. That didn't work out, so he entered the service to care for US army helicopter pilots and their families. And he was only in Vietnam until Omar Bradley – or someone – pulled him back out.

Fred's military career struck a chord with Thomas, who – like the other young men of his generation – had had to complete a period of military service. The West German army was trained to defend the country in case

Okan Toka

of an attack from the East. Thomas joined the parachute corps, then remained in the reserves for a long time. "They kept promoting me and promoting me, until ultimately I was appointed commander of "Medical Battalion B," in charge of 800 people in the Black Forest."

When he moved to Berlin, the reserves were reluctant to let him go – his commander offered him a choice of new battalions near the city. "I told them I was getting old and didn't want to jump out of planes anymore," Thomas says. "But I still have my uniform, in the closet."

For Fred, military experience translated into an incredible talent at organization. "When we began going to Turkey, the whole trip was organized like a campaign," Thomas says, "broken down into missions and 'sorties'."

When I accompanied the group to Turkey 15 years later, in 2009, I had the same feeling. I didn't know how much of the campaign had been planned by Fred Luft or Okan Toka, the young physician who was his former protégé. Okan was highly organized and in high gear, continually consulting lists and amending the timetable. He was clearly capable of the sort of "military" planning that Fred had demonstrated; whether those skills came from nature or nurture under Fred's tutelage was unclear. Surely a bit of both.

If you want to find a paradigm for the principle of "treasure your exceptions," Thomas Wienker says, you'd be hard put to find a better example than the description of the Turkish family in Bilginturan's paper. "There was plenty of evidence that hypertension had very complex molecular causes. The problem is to narrow the search, and the paradigm has been to find monogenic diseases in which such conditions are disrupted. The genes that are responsible are also likely to play a role in the much more complex phenotypes."

Thomas was to start working under the heading of "Genetic Epidemiology," and his first challenge was to learn statistics. "I'd never studied mathematics – of course I had attended a few seminars, but it wasn't my degree. Whatever I know about statistics today I learned from a member of Jens Reich's group named Willy Schmidt. A quiet man, not ambitious, but absolutely brilliant. He had worked in the former institute in Berlin-Buch in GDR times, along with Jens and several other colleagues, and had survived the changes. Every day for an hour or so we'd sit down and he would interrogate me. 'What are moments of a function? What are the first moments, the second moments, and how do you calculate them? What is a characteristic function?' It was intense and highly concentrated, and I'm very, very grateful for this."

Those skills would soon come in handy; Thomas' arrival rounded out the team that had been collecting around Detlev Ganten, Fred Luft, and Herbert Schuster. It took him a few months to settle in. Then the seeds he had planted – his late-night work in the library, the discovery of Bilginturan's paper, and the note Fred had taken during his talk – began to bear fruit. Fred decided that the time had come to tackle the Turkish story.

HakanToka

9 A sort of Shangri-La

The paper Thomas Wienker had found, written by Nihat Bilginturan more than 20 years before, was gathering dust in the archives as Bilginturan went off to practice medicine in the United States and to establish a medical school in Saudi Arabia. Over time he had lost touch with the family on the Black Sea.

Fred Luft and his colleagues knew none of this. They didn't even know whether Bilginturan was still alive. There was no way to contact the family without him – per standard practice, the article had given neither their names nor exact location. If he couldn't be found, the project would end before it ever began.

But his name still appeared on a faculty list from Hacettepe University, so Thomas made the first attempts to reach him by phone. That proved to be impossible. He could never get anyone who spoke English or German on the line.

"Eventually I reached the operator, and finally I managed to get an extension number," Thomas says. "Bilginturan had extension 22. A Turkish colleague taught me the word for *please* – I had to say it so often it will be stuck in my brain forever. *Lutfen, lutfen*. I would yell into the phone 'Lutfen 22' and sometimes they would transfer me and sometimes they wouldn't. But I never got through. Reaching him by telephone was a dead end."

Thomas had been lucky – and diligent – in finding the paper in the first place, and now luck would step in again. Fred remembered that when Herbert Schuster had moved to Berlin, he had brought along a Turkish doctoral student. He went to see Herbert and thus met Hakan Toka for the first time.

Sezai Toka had arrived in Munich in December 1962 at the age of 21, with the first wave of Turkish workers that had come to Germany under the agreement made by the two governments. He had just completed his military service in his home country. His future wife, Birsen, came to Germany with her father as a 13-year-old in 1966. "Her father 'slightly' exaggerated her age – saying she was 18 – so that she could come along and be employed in a German factory right away," Hakan Toka says. "They settled in Nuremberg but moved to Munich a couple of years later. My mother and father met there; they were working at the same BMW factory and were introduced by friends."

Sezai and Birsen were married in 1970; Hakan was born in 1971 and his brother Okan a year later. At the time they had an apartment with a single room. It was virtually impossible to find anything more spacious, so the German immigration officials asked the Tokas to send a child back to Turkey. Thus at the age of one, Okan was taken to live with his grandmother in Eastern Turkey, where he lived for a year. "My mother suffered a lot without him, and he didn't have it very easy, either," Hakan says. "When he returned he was sickly, but he recovered well. As a result, ever since we were little kids, I have been protective of him, and he has been the same way with me."

While there was a sizeable Turkish population and Turkish schools nearby, Hakan's parents were strongly convinced that their children needed to be integrated into German society. "It was important for both of them that we gain a certain independence from the immigrant community," Hakan says. "They put a lot of effort into this. They put us into German schools and even though we did well, they went to all the parent-teacher conferences."

Education was a top priority for their children: neither of the elder Tokas had had more than five years of school because their own parents hadn't been able to afford it. That wasn't unusual in Turkey in the 1950s. Hakan says that at the age of 71, Sezai Toka still regrets not having had more schooling. "I think that's why my parents were so determined that Okan and I would get an advanced education." He's grateful: Almost none of the children of other guest workers that they knew graduated from high school, let alone received higher education.

The Tokas managed this while working very hard on the BMW production line. They worked for more than 20 years on opposing shifts so that one parent would always be at home with the children, so they didn't see each other during most of the week. "They were dedicated parents who took us to school and picked us up every day, never left us without supervision, and never allowed us to play with children or visit a family they didn't know."

His father retired early in 1992 after a heart attack and back problems; his mother worked 40 full years before retiring. Over the course of their careers his father was promoted to a supervisor position, responsible for oversight of the machines, and his mother eventually got a desk job documenting deliveries moving in and out of the factory.

As the first-born, Hakan was expected to live up to his father's strict expectations, while less was expected of Okan. In retrospect, Hakan says, neither was an ideal way of growing up. "I think both of us would have

Okan Toka

wanted it vice versa sometimes." But the two brothers looked out for each other. "We have a driven father and an angel as a mother, and I think that played a huge role in the way we turned out. My father definitely gave us a competitive edge, and my mother gave us our kindness. Okan and I are a reflection of them. I think Okan is kinder, more like my mom, and I guess I am sometimes more like my dad. That's probably why he and I get along so well."

The expectations placed on Hakan included his future career. "Going into medicine was never really a choice, or a conscious decision; it was what was expected from me, and I simply took it for granted. I was born to become a physician. In Turkey and other Eastern cultures, it's a huge goal to get your kids educated, and to get them into medicine. Especially for the first-born. So when I got to the fifth grade my parents decided I should go into the 'Latin' track at school."

Even now, children in most German states are "sorted" into different types of schools after the fourth grade. At that point they enter a program that they usually remain in until they finish the equivalent of high school. The *Gymnasium* is open to those with good grades and is generally the route for those who go on to the university. After a year or two the children are further sorted into sub-tracks on different themes, with a fairly rigid schedule of obligatory courses and a few elective ones they will pursue until the end. In the 1970s and 1980s most schools had a program that emphasized Latin – a lot still do. Parents often put their children into it in hopes that they will become doctors.

Hakan survived nine years of Latin and finished high school with outstanding grades. That was crucial; entry into medical school in Germany is highly competitive, as Ramin Naraghi's high school friends had found. Hakan's grades were so good that when he applied to medical school at the University of Munich, he ranked first out of all the foreign applicants who had completed high school in Germany.

He still wasn't a German citizen; under curious laws regarding nationality, that title was extended only to the children of parents with German passports. This policy led to ludicrous situations, as when people who broke the law were deported to a country where they had never lived. Later the law would be changed to allow the children of immigrants to choose their nationality at the age of 18. That option wasn't open to Hakan, who had been born in Germany and was raised completely in this environment, until the age of 26.

Even then, the process was not easy. "It took two years," Hakan says. "Under the law, I first had to be released from Turkish citizenship. And Turkey wouldn't release a young man until he had served in the army. I was lucky that I had always lived and studied abroad, so I could fulfill the requirement by attending a sort of basic training camp that only lasted four weeks. Even then, I only escaped seventeen more months of service by paying the 'small' fee of 10,000 German marks. My parents paid it – yet another sacrifice they have made for me."

Hakan's younger brother Okan followed two years later, entering the same program in Munich, with grades that were just as superb. "Part of my interest in medicine was due to sports," Okan says. "I played a lot of soccer and had a lot of injuries." Then there were long talks with his brother, who filled him in on the life of a first- and second-year medical student. It sounded fun, Okan says.

Both young men received prestigious scholarships while attending medical school; Hakan from the Friedrich Ebert Foundation and Okan from the Bayerische Hochbegabtenfoerderung (a foundation that supports extraordinarily talented students).

Attending the same medical school brought them into frequent contact. "When Okan took second-semester anatomy, I was tutoring that class," Hakan says. "I'd

done pretty well in my own anatomy course and it was a well-paid job. I was an instructor for 24 students, who worked on three corpses at a time in groups of eight; my role was to prepare them for tasks and tests. Okan wasn't under my supervision, but sometimes I'd go over to his table and help out with questions and tasks on the corpse. We were always a team, and used the opportunity to study anatomy – I was refreshing my knowledge while he prepared for tests."

Okan's future wife, a German medical student, was also in the class. "Apparently she disliked both of us because she thought we were too confident and a bit cocky," he laughs. "Obviously she changed her opinion – at least about one of us!"

By chance Hakan landed in a class that Herbert Schuster was teaching on the physical examination of patients. He needed the course to fulfill a research requirement for his degree. It would mean joining a lab, picking a topic, and doing a project. Herbert had briefly mentioned some of his scientific work during the lectures, and Hakan was impressed by his teaching. Hakan was an active participant and caught Herbert's attention. One day after class, Herbert approached him about the possibility of doing a project in his group and invited him to come by the lab.

There they talked about a recent paper on the genetics of a condition called "familial hypercholesterolemia." "By chance, my father suffered from hypercholesterolemia, so it was my first real encounter of the intersection between basic research and something human and personal," Hakan says. "That tweaked my interest, and the people in the lab were very nice. So we agreed that I could do my thesis there."

Under Herbert's tutelage, Hakan began to master some of the basic molecular techniques needed in the lab to study familial hypercholesterolemia. "It's a genetic disease that is inherited in a dominant fashion and affects approximately one in five hundred individuals in the general population," Hakan says. "People who have it often suffer heart attacks at young age and need to be treated aggressively with cholesterol-lowering medications to protect them from fatal cardiovascular disease."

The lab work gave Hakan a new perspective on the concepts he had learned in his biology courses. Although scientists often talk of "genes" and "proteins" as if they are individuals, like characters in a film or play, single molecules are usually invisible, undetectable, and useless. Doing anything meaningful with them requires obtaining millions or billions of copies.

The first step along the way is to extract DNA from cells in a process called *precipitation*. One of the main components of the DNA molecule is phosphate, an acid with a strong negative charge; this makes it highly reactive, and by putting it into a chemical bath with a positive charge, chemists can draw the molecule out of a liquid solution. Hakan mastered it so well that he says he set a lab record in precipitating DNA.

Once the DNA has been extracted, it has to be copied – another technique Hakan learned from Herbert. The method by which this is done is called the *polymerase chain reaction*, or PCR. Until 1983, DNA amplification was mainly carried out in cultures of bacteria and it took weeks. But in that year a young chemist named Kary Mullis, working at the Cetus Corporation in California, figured out a way to achieve it in just a few hours. PCR quickly became such an essential tool in research that science journalist Nicholas Wade, writing in the *New York Times*, said that biology could be divided into two eras: "before PCR and after PCR." It became such an essential tool so quickly that Mullis was invited to Stockholm to collect the Nobel Prize in Chemistry. They were awarding it to a wildly colorful character, even more colorful than James Watson, and that's saying a lot.

Every scientist gives a lecture upon receiving the Nobel Prize, and Mullis' remarks begin with a reference to Erwin Schrödinger and Max Delbrück. Mullis highlights the way Schrödinger's popular book *What is Life?* inspired the first molecular biologists. Then he cites the Nobel lecture given in 1969 by Max Delbrück, who bemoaned the fact that most scientific research "addresses an infinitesimal audience of fellow composers… (A scientist's communication) is modified, amplified, fused with the results of others, and melts into the stream of knowledge and ideas which forms our culture."

The point, Mullis continues, is that explaining science to the general public is hard. While he promises to do his best in describing PCR, he warns, "I do have to say a few things that are going to be difficult."

First, however, he dives into an entertaining account of his childhood, of wandering through "an undeveloped wooded area with a creek, possums, raccoons, poisonous snakes, dragons, and a railroad track," and of exploring the labyrinth of storm drains under his hometown of Columbia, South Carolina. Then he turns to the real obsession of his childhood: building rockets, culminating in the successful launch of a frog a mile into the air. The animal returned alive.

Mullis goes on to recount a long series of adventures in life, love, and the invention of PCR, intertwined in a way that provides a unique account of the creative process of science (at least Mullis' creative process). Nicholas Wade wrote, "For those who would like to analyze creativity and sell it in bottles, Dr. Mullis would seem a promising subject…Yet the Mullis formula for creativity, on closer inspection, is a brew probably somewhat unsuitable for general consumption."

Most of the insights came during long drives through the countryside with his girlfriend of the moment – and he carefully correlates the ups and downs of his ideas with the mood of his companion. The talk contains only one reference to LSD during a description of an encounter with Albert Hofmann, who invented it, at the house of a friend. A few years later Mullis went on the record to claim that regular use of LSD was a major contributor to the creativity of his thought processes.

He said the drug wasn't, however, responsible for a long conversation he once had with a glowing green raccoon in the woods of California. He couldn't explain the raccoon, or its ability to speak English, but later said "that multidimensional physics on a macroscopic scale may be responsible."

The various careers he tried on the way to a Nobel Prize included research, for which he eventually received a number of patents. They didn't always pay off as well as they might have. Cetus Corporation, where he worked when he invented PCR, paid him ten thousand dollars for his discovery. A few years later they turned around and sold it a few years later to the Roche Molecular Systems company for 300 million dollars.

Prior to Cetus, Mullis had managed a bakery and tried his hand at writing fiction. "Fiction is my way around doing experiments," he told Nicholas Wade. Take the concluding paragraph of his Nobel speech, which reads a lot like the end of a short story:

> *In Berkeley it drizzles in the winter. Avocados ripen at odd times and the tree in Fred (Faloona)'s front yard was wet and sagging from a load of fruit. I was sagging as I walked out to my little silver Honda Civic, which never failed to start. Neither Fred, empty Becks bottles, nor the sweet smell of the dawn of the age of PCR could replace Jenny. I was lonesome.*

As Werner Heisenberg said, and Thomas Wienker quoted, "Science is made by men." Even, sometimes, some very strange ones. And, as Fred adds, "Some pretty impressive women, as well."

Such was the mind that conceived the polymerase chain reaction, the game-changer in molecular biology and a method that would be used constantly in Fred and Herbert's labs. The method is based on the process by which cells copy their DNA every time they divide. Watson and Crick had shown that DNA consists of two complementary strands (today known, appropriately, as "Watson" and "Crick").

In living organisms, managing the copying process requires a huge number of molecules that drive the cell through cycles of rest, DNA duplication, and cell division. It's simpler in the test tube. First you heat the DNA molecule to separate the strands, a process known as DNA melting, then add a DNA polymerase to copy them. To rejoin the new Watsons and Cricks, you cool things down again. Repeating the cycle over and over turns the test tube and its components into a copying machine that eventually makes billions of copies of an existing molecule.

The trick was to repeat the cycles of heating and cooling as fast as possible, but that was hard using common DNA polymerases. In cells, they were never exposed to the temperatures required to melt DNA; nature uses a different method to separate the Watson and Crick strands. Cooking the mixture usually destroyed them, or at least rendered them very inefficient.

The solution Mullis found was to use polymerases from organisms which thrive at much higher temperatures. Certain types of bacteria, such as the *thermophiles* that inhabit the hot springs of Yellowstone National Park, have adapted to environments in which other organisms would be cooked. In the 1960s the American microbiologist Thomas Brock found species of such thermophiles in the hot springs of Yellowstone National Park. These organisms managed to copy their DNA under conditions of extreme heat thanks to a DNA-duplicating molecule called the Taq polymerase. One of the inspirations that struck Kary Mullis while driving down a California highway was to use this molecule as the basis for the polymerase chain reaction.

Molecular biologists weren't particularly interested in copying an organism's entire genome; their work depended on duplicating single, specific molecules. Mullis' second sudden inspiration was to realize that adding primers – specific, short DNA sequences found somewhere in the genome – would point the polymer to a precise place to start copying DNA. Adding a second primer, with a sequence that appeared farther down the DNA on the complementary strand, would tell it where to stop. With these tools, and a machine that could cycle between high and low temperatures at controlled intervals, researchers now had a quick way to make billions of copies of any segment of DNA.

There was still one problem: you had to figure out where a particular gene was located among the 46 human chromosomes, and then identify two unique bits of DNA code that flanked it. You needed those two sequences to make the primers. This was one of the hardest parts of the process; it was called molecular cloning, and it was a major activity in any lab hoping to study a particular gene.

This was so hard that in the early 1990s a scientist could build a whole career on the successful cloning of a particular gene. Doing so required the participation of a team of researchers with good technical skills. Hakan's success in mastering techniques such as DNA precipitation and PCR made him a highly-valued member of the lab. So much so that when Herbert Schuster was offered a position in Berlin-Buch, he invited Hakan to come along.

To contact Nihat Bilginturan, Hakan first tried the phone number provided by Thomas Wienker. The calls landed in the office of the pediatric endocrine unit at Hacettepe University. He did finally manage to get in touch with Bilginturan, who worked there, but on the phone the physician didn't sound very friendly.

"He knew that someone had been trying to get in touch with him," Hakan says. "And while he promised to think about our proposal to revisit the family, he didn't sound very interested."

"I'm very busy," Bilginturan told him, "and it's the season for the tea harvest, so the family is completely occupied with that." It was a clear brush-off.

Hakan was frustrated. The problem might somehow be cultural – having been protected from becoming "too Turkish" during his childhood, he wasn't comfortable with the intricacies of social relationships that might be affecting the situation. So he called his father for advice.

That call turned out to be more profitable than Hakan expected. By chance, his father said, he had a cousin who was also a pediatrician in Turkey. "He's a big-shot," he said. "Maybe he can help. I'll give him a call."

His father called Muzaffer Kurkcuoglu, the relative. It turned out that the cousin and Bilginturan had a lot in common: both were prominent pediatricians, and both had spent time in the United States. The circle of eminent pediatricians in Turkey was small, and Kurkcuoglu immediately said, "Of course I know Bilginturan. He was once a student of mine."

That sounded promising, but it would still be necessary to contact Bilginturan directly, and Hakan realized it wouldn't be achieved by telephone. He recounted the conversations to Fred Luft. "I think the only thing I can do is fly there and talk to him face-to-face."

If you ask Fred Luft how he has managed to fund a project over 20 years, despite periods of seeming hopelessness, he'll tell you ironically that a lot of it has come from his VISA card. Now he trotted out the VISA card for the first time, pressed it into Hakan's hands, and told him to go to Turkey.

"Do whatever you need to do," Fred said, "just meet with him and try to convince him to work with us. Emphasize that we want to collaborate with him, we're not out to steal his work." So Hakan booked a flight to Ankara.

Once there, things didn't go as smoothly as Hakan had hoped. He called Bilginturan from the city. "By chance I'm visiting family in Ankara; maybe you could spare five minutes for me."

Bilginturan agreed, which was a big relief, but Hakan was nervous going into the meeting. He had prepared as well as he could by writing a short document that briefly described the group and what they hoped to do.

"The meeting lasted for ten minutes and took place in his office at the hospital," Hakan says. "I don't know whether my relative had already been in touch with him. Bilginturan clearly knew Kurkcuoglu's name when casually dropped it into the conversation, but he was very formal – a bit stiff – the whole time. Thinking back, I must have seemed like a crazy, overenthusiastic medical student."

Hakan left without getting a sense of Bilginturan's true level of interest. "Once again he promised to think about it. I think he was a bit burned because at some point earlier he'd been contacted by a French group with a similar proposal, but they had been rude. Basically they'd asked him to go back to the family, collect blood samples, and send them to France. As if he were some sort of technician and delivery service, at their beck and call."

The next day Hakan flew back to Germany. "I told Friedrich Luft that things had gone well, but honestly I wasn't so sure. I'd been as polite as possible to him, and

stressed that we were both a credible group of researchers and were interested in carrying out the project in a collaborative manner. It was the most any of us could do; now we just had to sit back and wait."

Later his brother Okan got more of the story from Bilginturan. "Muzaffer Kurkcuoglu called him and said, 'You know you were speaking to my nephew, don't you?'"

Bilginturan hadn't known, but the combination of Hakan's visit and the call worked their magic. Within two weeks of the visit, Hakan had a response. He can't remember whether it came by phone or letter, and he can't be sure how the Turkish physician actually made his decision. Part of it, surely, was the Berlin scientists' willingness to integrate the physician as a full-fledged collaborator, but the efforts of Muzaffer Kurkcuoglu may have been just as important.

In any case, the response was positive. Not only was Bilginturan willing to cooperate – he had contacted the family in Karamat, and they were willing as well.

"Basically when he contacted me he asked, 'When are you coming?'" Hakan says.

The annual tea harvest had ended and soon the family would begin on their second crop, hazelnuts. It meant that Fred Luft and his colleagues would have to travel to the Black Sea, and they would have to do so within a defined window of time. Fred needed to find a way to finance the trip, leaving Hakan to organize a plethora of practical details.

The MDC wasn't yet in a position to fund the expedition; there ought to be other ways. Detlev Ganten was basically supportive, but Fred wasn't in the mood to hear the "Das Geld liegt auf die Strasse" speech again.

"I knew a somewhat strange American captain from the Air Force who had come by and told me about 'NATO grants,' which might provide funding for special projects," Fred says. "The application process was – thank God – straightforward and fairly simple, and I think I wrote up the proposal over a weekend. We sent it off, and very quickly they said, yes, they'd finance this crazy trip. They gave us 20,000 dollars, part of which was used to pay my VISA card debt, and that's how the project started."

As the only Turkish speaker in the group, Hakan realized he needed help, so he called his brother Okan. "Hakan had just left Munich with Herbert Schuster in the beginning of 1994," Okan says. "He'd kept me up to date on the project and in the summer he called me up, gave me more details, and said they were planning to do fieldwork. Another Turkish-speaking student would come in handy, and they thought of me. Well, I was facing a lot of hard exams, and I told him that. I said, 'It sounds nice, but first I have to take my exams, and then we'll see.'"

Hakan reported back to Fred, whose response was, "Well, okay, let's wait for him." In the meantime they could start organizing everything. Okan finished his exams, Hakan convinced him to come and was extremely grateful when his brother arrived.

In his first meeting with Fred Luft, Okan was just as inspired as everyone else had been. "I went into his office and he immediately greeted me by my first name," Okan says. "He made me feel like he'd been waiting to meet me a long time. As a med student you always see these big professors, and they're always impressive. You don't say much; you listen, and you hang from every word that emerges from their mouths. Within five minutes I knew that this was someone stamped from a completely different mold."

He had already met Herbert Schuster, "another very impressive physician," and spent time talking to Sylvia and Hakan about the specifics of the project they planned to do.

Now Fred told him, "It's nice that you're coming along; it's going to be fantastic. I'm an old guy, and I've done a lot of things, but this is going to be something really special for me, too. Field work is something that you'll remember forever."

"He was so enthusiastic about what we were going to do," Okan says, "that I was completely convinced we were about to do a great thing." The feeling would return much later when Fred confronted him with a much greater opportunity.

Within two weeks the brothers, Fred, Herbert Schuster and Thomas Wienker had worked out the details of what needed to be done. Hakan and Okan helped organize all the equipment they'd need for the field work. It was an extensive collection. "We needed syringes to draw blood, tubes to store it, cameras and film to photograph the family's physical features at a quality that could be published in a medical journal," Hakan says. "Then there was equipment to test urine for signs of kidney damage that is typically caused by hypertension, and automated machines to measure blood pressure and print out the values that were obtained."

If any of the equipment failed during the trip, there was no guarantee it could be replaced it in Turkey, so the brothers tested everything extensively on each other. "We photographed each other's hands, feet, teeth, and faces – all the body parts of interest, and yes, my brother made faces while we did it," Hakan says. "We practiced obtaining the medical data under approximately the field conditions we expected to find."

Finally, Hakan and Okan also purchased the group's plane tickets and bought gifts for the Turkish family. Once again Hakan called his parents for advice – he didn't have a good sense of what gifts would be useful or appropriate. It was hard enough to pick out presents for the birthdays of his relatives; what on Earth would you give to a farmer from an area of Turkey you'd never visited?

Some of the recommendations seemed a bit odd – dozens of tubes of German toothpaste, for example – but they turned out to be right on the mark. The other choices included body lotion, thin socks for the men, and colored pencils for the children.

When everything was ready, the group drove to the airport in Berlin and checked in their boxes of equipment, which would somehow have to be muscled through Customs on the other end. That might pose problems, but Fred was more worried about the trip back, when they'd be bringing along blood samples. For now they boarded a plane for Istanbul and the connecting flight to Ankara. Once they had collected Bilginturan, whom only Hakan had met so far, they would take another flight north to Trabzon, on the Black Sea.

There were five along on the trip: Fred Luft, Herbert Schuster, Thomas Wienker, and Hakan and Okan Toka. I doubt that anyone who witnessed the departure of this odd assortment of individuals, of mixed nationalities, ages, backgrounds, and professions, could ever have guessed what they were up to.

And while the members of the group were excited about their first crack at genetic fieldwork, none of them guessed how strongly this journey would affect them, or that it would become a definitive landmark in their lives.

The first readers visited the kingdom of Shangri-La in 1933, when it magically appeared in the mind of author James Hilton and in the pages of his novel *Lost Horizon*. Shangri-La rests in a mythical valley, deep in

the Himalayas, where its inhabitants live peaceful, harmonious lives in complete isolation from the rest of the world. The few outsiders who ever find this utopia do so by accident; once there, they should never leave. It can never be found a second time – well, almost never, depending on how you interpret the ending of the novel.

For an outsider to think of Karamat as a utopia is surely naïve and would likely make any anthropologist shudder. Many of its residents can personally remember the severe poverty of the past, when their main crop was corn, and they grew barely enough of that to meet their most basic needs. Here, in great contrast to Shangri-La, whose inhabitants are blessed by perfect health and sometimes live for centuries, the opposite was true. Those suffering from Bilginturan's syndrome could expect a lifespan nearly two decades shorter than that of other family members.

Certainly not everyone living in the village is content. Some have left for the city, pursuing jobs and an ideal of a modern, more luxurious life. Here the work is hard, particularly during the harvest season. But many have left out of need rather than choice, as the property of their parents has been split into parcels too small to support all the children. Sometimes the problem is handled by alternation: One brother works the farm while another finds a job, and the next year they switch turns.

Despite these realities, this place has an innate charm. At intervals along the road are immense rhododendron bushes, as vast as small forests. Thick tea bushes carpet the dips and rises, interrupted by dusky brown stretches of hazelnut trees. Most of the houses are simple structures spaced at wide intervals along the hills, or tucked into niches between them; the sides of the road are adorned by rough huts of weathered wood whose slats have been hammered together in vertical and horizontal patches. They store grain for the animals, and most stand on stilts. The legs are capped by what look like big metal funnels, wide sides down, to keep rats and mice from running up and getting into the stores.

Along the gravel road to the coast, there is always someone walking up or down. They don't seem hurried. We were all struck by a sense of harmony between the people and their land, and by a lifestyle that seemed free of that modern species of stress which seemed to permeate our own situations back home. There are few places where life still moves at the pace of a century ago, or two, or ten. Cafer says his family has inhabited the region for at least 500 years, and probably much longer.

By 2009 many of the villagers had cars, but they would find it ridiculous to drive down to the city on a daily basis. Now the houses have Internet connections and televisions, often tuned to a soccer match, or soap operas that seem incomprehensible to visitors for both their language and their style. But modern devices seem to have been integrated without breaking the flow of some fundamental rhythm of life. The children complain that their friends in town are too preoccupied with their cell phones to play. Here they would rather run around outside, chasing animals or each other up and down the hills.

And perhaps there is something innately healthy and sustaining about a rhythm in which even the hardest work is interrupted at regular intervals, five times a day, for prayer. The workers pause in the fields, take a moment to clear their minds, and kneel to the ground. For a moment the air fills with the music of incantations that rise from the spires of the minarets. The voices of the mullahs quaver as they roll over the hills in an ornamental style whose purpose, as they praise Allah, seems to be to stretch each phrase, to stretch time itself.

One aspect of this place did, in fact, call to mind Shangri-La: The moment you leave the coastal highway, you hit a series of gravel roads that twist and fork in labyrinthine patterns. For a week in 2009 we followed this route

every day from our hotel to the village, but it seemed impossible to decipher. The only way I could ever find my way back would be by luck or accident. Fortunately we had guides to drive the big red van: Mehmet or Cafer, or Okan – who got plenty of practice learning the route when, later, he lived here for a year.

This sense of peacefulness was probably expressed best by Ramin Naraghi. He hasn't been back to Turkey for 15 years, but he was anxious to know how the family was faring. "You could see that progress was creeping into their lives," he said. "I hope, I really hope, that they haven't paved the roads to the village." (So far they haven't.)

"Some of the youngsters wanted that to happen so they could make it into town faster; they were drawn by the city," Ramin says. "The old generation didn't want it to happen, and they were right. As soon as it does, it will be so much easier to drive up there – too easy – and everything will change. They'll lose their independence and identity. The area is so beautiful – the tea plantations, and the magnificent view of the Black Sea from up in the hills, over the rolling landscape. Rich people will try to buy up the land, build extravagant houses there, and displace the population. That would definitively destroy their world.

"It's a hard life, but for all the things these people lack, they have one great treasure – they own this land," Ramin says. "If they were to lose it, everything would change. That would be a great, great pity."

If the first trip to Karamat required a lot of organization on the part of the scientists, equal preparations had taken place in the village prior to their arrival. After Bilginturan's call, and the establishment of the date when the group would come, nearly 60 people from the villages and surrounding areas had to be mobilized to make the study possible.

Kemal had died in 1991, of a stroke caused by high blood pressure, so Bilginturan called a member of the family with whom he had had the most direct personal contact over the years: Kemal's brother Ali. Since the early 1960s, when Kemal took him along on those first trips to the doctor, Ali has been crucial in supporting the scientific research into Bilginturan's syndrome from the family's side.

Okan Toka got to know him well later. "Ali's involvement has been crucial since the beginning," Okan says. "He has always been very deeply engaged in this issue, he knows a lot of doctors, and he likes to talk!" Talking was crucial because of the way the family makes decisions and resolves conflicts.

"Every branch of the family has a leader, more or less," Okan says. "Usually it's a religious figure like Kemal or Cafer, or the oldest man in a group of families. If the father or grandfather is alive, he's pretty much the person who tells everybody what to do and what not to do. When a problem arises, they usually take it to him and they respect his decision. Ali is one of these guys; he occupies an important place on one branch of the family with the syndrome. He was eager to work with us the whole time."

Cafer was much younger but had followed in the shoes of his father Kemal. In 1994 he was 28 years old and had become the community's Hoca. "Cafer didn't inherit the syndrome, and his wife comes from somewhere else, so of course their children aren't affected," Okan says. "But at every stage of this study we needed unaffected family members, and so his family has been important for research reasons. Determining what genetic factors make a person sick requires eliminating the factors that don't. And Cafer has played an absolutely crucial role all

along in organizing things and getting the whole family to participate."

Cafer had arranged for the scientists to work from his home, which was situated on the highest peak of the village. Adjacent to the house was a large paved area that would soon overflow with hazelnuts, once the harvest began. A large barn bordered one side of the square, and across from it was a small prayer house. The fourth side was open to the hills and a panoramic view of the Black Sea.

Cafer and his wife had cleared out the prayer house and installed a table and chairs. Twenty years before, during Bilginturan's first visit, one room had sufficed for the interviews, blood pressure measurements, and photographs. But the investigations that Fred Luft and his colleagues had planned were more extensive, and most of Cafer's house would be needed.

On the way the scientists had stopped over for a night in Ankara, where they had their first meeting with Bilginturan. It took place in a café; they drank coffee and black tea and made the first tentative stabs at getting to know one another. "He was a pleasant, rather formal fellow," Fred says. "He'd agreed to meet us and take part in the project, but you could tell there was still some hesitation." Reluctant or not, the aging physician accompanied them to the airport. Once more, they went through the drama of checking in their boxes of equipment.

Cafer got an inkling of what was in store for his family when he picked up the scientists in Trabzon. Even though he had borrowed a large van for the occasion, it took a while to load everything at the airport. It was like putting together one of those wooden puzzles whose pieces are cut into odd shapes; assembled correctly, they form a proper cube. But you usually have to try several times until you get it right and eliminate all the protruding ends.

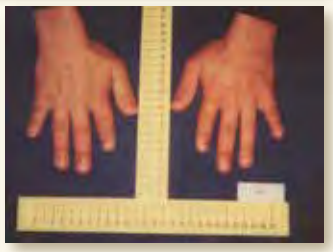
Within about a minute of their arrival, Fred realized that language was going to be a severe problem. Cafer spoke absolutely no English – he couldn't understand a single word they said. And this was probably the most highly-educated member of the family. Granted, that education had been focused on the Islamic religion, but still…

Intellectually, Fred had accepted the fact that they would need translators, and between the Toka brothers and Bilginturan there were enough to go around. They'd been told, "The family doesn't speak English or German," but in most situations that didn't mean an absolute language barrier. People said that about France, too, and then you got to Paris and discovered they had Disneyworld.

Here they were facing the kind of situation that Thomas had encountered for weeks and weeks on the telephone. It was troubling because Fred was fully aware of the extent to which physicians depend on verbal descriptions; often you needed to pick up subtle cues that might not translate very well across linguistic or cultural boundaries. If you could talk to somebody, you might not be able to read his mind, but you could usually sense when he was avoiding something, hiding something, or telling an outright lie. If you couldn't understand a word he said, though, there was no telling what a person might be thinking.

And the project that Fred, Herbert, and Thomas had in mind would require a family history of exquisite precision. To get the kind of pedigree they wanted, and the medical details they needed, the scientists were going to have to ask a lot of questions. Some of them would be deeply personal and not much fun to answer.

At least Bilginturan's English was fine. A bit rusty, but fluent – after all, he'd spent time among the natives in Boston and Missouri. That wouldn't be a problem; the



dust would surely shake off in a couple of days. And he was pleasant enough.

But he was stiff, very formal, even with the Tokas. "Maybe it was a cultural thing, or a status thing," Fred says. "We probably seemed like a crazy bunch. He was surely worried about protecting the family and maybe his turf, too."

Well, he thought, Bilginturan doesn't know us yet. We'll give him a few days. Once he's convinced that our motives are pure, maybe he'll come around.

When the group finally arrived at Karamat, the van had to be unpacked again. Cafer's wife and young son and several of their relatives were waiting at the house and watched the process with a mixture of curiosity and awe. They'd never been to the circus, so they'd never seen a tiny car disgorge an impossible number of clowns. But this was fine entertainment that they seemed to find just as hilarious. Just when you thought the last box had been unloaded, here came another, and another, and another.

Cafer's wife didn't find it all that funny; she was rearranging furniture in her mind. Some of the equipment went into the two small rooms of the prayer house, and the rest would have to go into their living room, or one of the bedrooms.

Everybody was wondering what might be in so many boxes and was curious about everything that emerged. Many years later, Herbert Schuster said, "They were 'technology believers;' they spent hours inspecting our automatic blood pressure machine. They thought if we hooked them up to such a machine, it would somehow make them immortal."

Less exciting, he said, were the hours of questioning they would be put through. Or taking the blood and urine samples. "But if you'd left them hooked up to a blood pressure machine for hours on end, they'd have been perfectly happy – watching the cuff fill up with air and slowly deflate, watching the lights blink and listening to the beeping sounds. And then the printer hummed and out came the ribbon of tape with the values that had been measured."

By evening, Herbert and the Tokas had an overview of where everything was, and relatives were arriving at a steady pace. Some of the new arrivals bore the traits of Bilginturan's syndrome. It was the scientists' first encounter with the condition they had come to study.

You couldn't see any direct symptoms of the high blood pressure, but there was no mistaking the small hands – you couldn't help looking – or the fact that those family members were a head shorter than their relatives.

Cafer had greeted Bilginturan warmly at the airport. Some of the older people remembered him from 20 years before. Thomas noticed that they treated him with reverence and awe; in the family, he had a bit of a mythical status. "Apart from studying their condition, he had given them the advice to grow tea and hazelnuts, and they had done very well," he says. "You could tell that they trusted him completely."

As for Bilginturan's own behavior, Thomas Wienker noticed the sort of aloofness that had been bothering Fred. "He had the comportment of a gentleman; later we understood that there was a bit of a class sensibility involved. Perhaps he was concerned that his role be respected… My impression was that he wasn't yet wholly there, hadn't yet made a complete commitment to the project we wanted his help with. The rest of us were burning with ambition and completely immersed in things. He stayed a bit distanced."

A lot had been going on in the kitchen as the group unpacked, and now they all took their places for dinner.

A low table had been set up outside and Herbert had another surprise.

"The men sat in a row on either side of the table on the ground. There was plenty to eat, but the women didn't join us. They stood behind the men and served and didn't eat. What especially irritated me was that the men ate while the women watched, and when they finished it was time for the women to eat. I don't think they were going hungry – they'd probably already had something in the kitchen. But it was hard for me to sit there and watch this."

It gave him a greater appreciation for the traditional style of European families, where people wait to begin eating until everyone has been served regardless of gender. "But there's a trend in modern families in Germany that our hosts would have found equally shocking: everybody goes to the fridge and gets something and takes it to the TV to eat. In doing so they lose an important social tie."

After dinner it was time to give the family an idea of what they would experience over the next few days. Thomas would work with Bilginturan and the oldest members of the family to review their relationships in painstaking detail, adding to the original pedigree and possibly correcting it. In essence, they would be starting from scratch, using Bilginturan's original "map" of the family as a reference in case something was unclear.

Fred would take pulse and blood pressure measurements and would carry out a medical exam of affected and healthy family members. Bilginturan's original paper had convinced him that they would be seeing a true case of essential hypertension, but he wanted more evidence. And anyone who had suffered from such high blood pressure for so long was likely to have experienced other problems – an increase in heart size, kidney damage, problems with blood vessels, and so on. Those conditions needed to be detected and recommendations for treatment needed to be made on an individual basis.

Herbert, and Okan would draw blood samples and measure the family's height and weight in a station they set up in the prayer house. Hakan's job was to obtain urine samples and take photos of the family members – their hands, of course, but their feet as well, also shortened by the syndrome. And teeth, and faces. Later, Ramin Naraghi told me that the genetic condition had a wider effect on bone structure that was noticeable, for example, at the back of the head. The segment of the skull above the spine was shorter than in nonaffected family members.

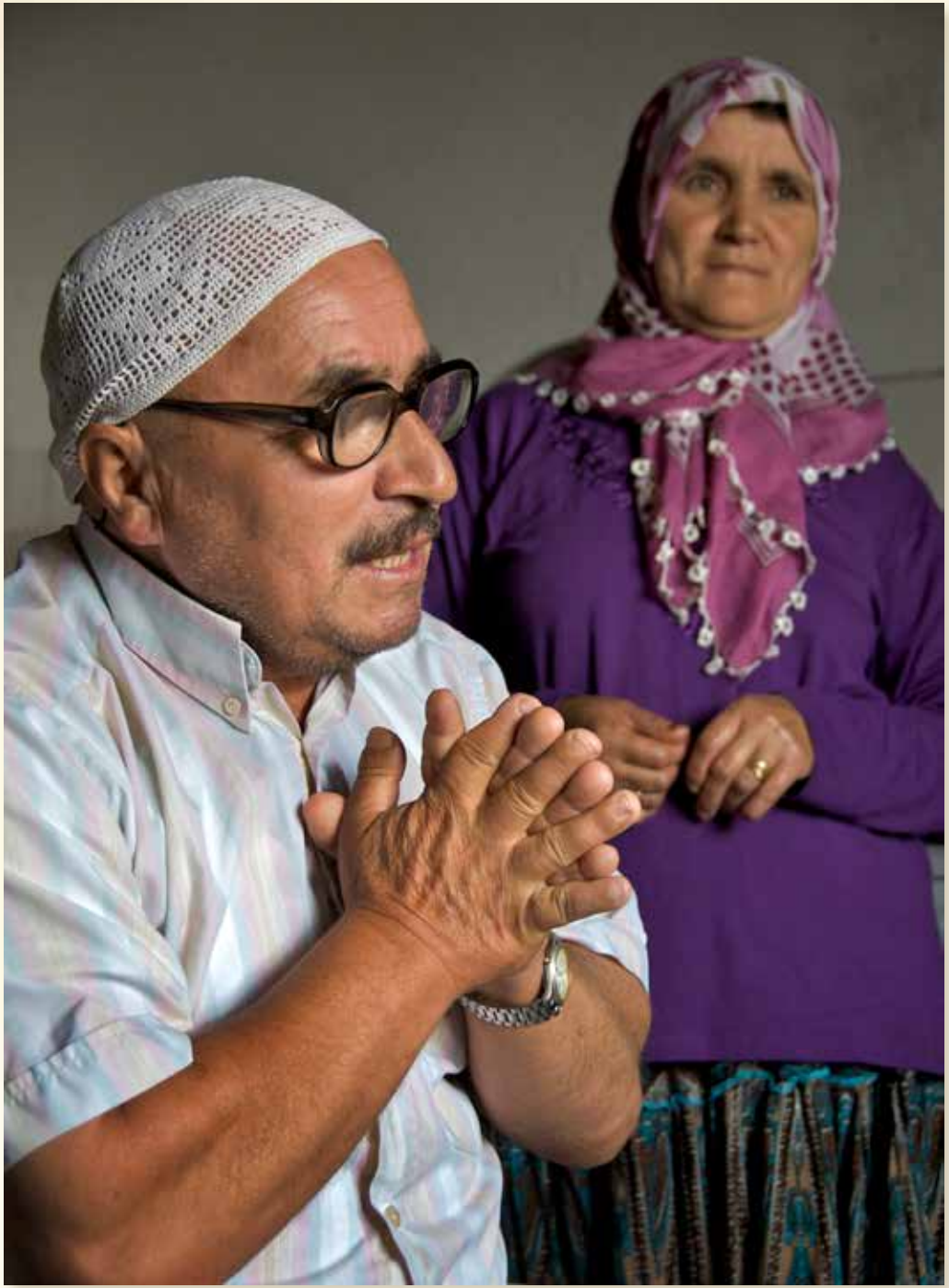
Hakan and Okan had constant double duties during the week – they would be permanently on call as translators. Bilginturan could help to an extent, but every interview would have to be translated and every procedure explained. While they did their own work, they would also be hopping from station to station.

Some of the family members looked queasy at the mention of drawing blood, and the mention of urine samples got an even poorer reception. But they seemed fascinated as the scientists explained the ultimate goal of their visit. Hakan and Okan translated as Fred and Bilginturan talked about hypertension, genetics, and the nature of genes and chromosomes.

"They were curious and open-minded and asked a lot of questions," Okan says. "They didn't understand any of the scientific jargon we typically use to describe these things, of course, but if you think about it, given who they are and how they live, they already had a working concept of some basic genetic principles. Here they stare you right in the face. The family is large, and they notice the fingers and their general short stature, and they also know that some of them are sick." They understood that the problems were passed somehow from one generation to the next, and that if you were affected, you had

about a 50-50 chance of having a child that would be affected as well.

"They also knew that it wasn't good for close relatives to get married," Okan says. "After six generations, you might expect to find some marriages between distant cousins that were affected, but as far as we know, that has never happened."



Ali and his wife

10 Lost colonies

Over the next few days, the scientists plunged into their work, sending their subjects from station to station. In the evening, Cafer or his cousin Mehmet would drive them down to their hotel on the coast, half an hour away. "We were exhausted," Hakan says. "But we'd sit there anyway and eat great Turkish food and drink Turkish wine and talk about what we were doing, sometimes for hours."

Early in the morning Cafer or Mehmet would pick them up in the van and bring them straight back to work. This rhythm would dominate the whole week. All along the way there were cultural barriers to overcome, some humorous, some that struck a deeper chord.

"I had never had such an intimate look into a foreign culture," Thomas says. "Hakan and Okan helped us fit in by giving us a sort of basic guide to behavior. Sometimes the issues were amazingly trivial. For example, there was a toilet that was basically a hole in a cement floor. Hakan told us that no Muslim man would ever use it while standing. Since it was a woman's duty to clean it, that went without saying."

The family wasn't always clear about the roles or backgrounds of the scientists. After Bilginturan, Fred Luft was the oldest, with Thomas Wienker coming in a close second.

Given the role of age and authority in the culture, it automatically conferred a certain status on Fred. But respect wasn't absolute. You could instantly lose it if they didn't trust you, or if something else got in the way.

"Among the family members there was a very old man," Thomas says, "and at some point he figured out that Fred was an American. 'We don't like Americans here,' he told me. I asked him why. 'Because they gave Jerusalem to the Jews. So I will never talk to him.' And he didn't. Instead he turned to me as the next oldest, the second 'honorable person,' with whom he was willing to discuss life and death and everything," as translated by Hakan.

Fred was determined to carry out a very careful medical examination of each member of the family, both affected and those who were not. There were several reasons. "This village was so remote that they rarely saw a doctor, if at all," he says. "So they were lacking basic medical care."

Another reason, Thomas says, is that any genetic condition usually affects individuals in different ways. "That's because they are individuals who often have other features that influence the development of any given condition. And we simply had to clearly determine who had the symptoms of a particular syndrome and who does not, defining the symptoms as precisely as possible."

Two accomplish this in a human genetic study, two factors had to be assessed. The first was *penetrance*, which refers to a connection between the form of a gene that a person inherits (his *genotype*) and the *phenotype* – the set of characteristics or symptoms associated with it. Later the scientists would prove that everyone in the family who had inherited a specific segment of DNA developed radically high blood pressure and a specific type of short fingers called brachydactyly type E. They already expected that this was the case, but at the moment, this remained a hypothesis.

Complete penetrance seemed likely, given the pattern of heredity mapped out by Bilginturan, but you couldn't be sure. Someone might have inherited a gene normally associated with the defect but show no symptoms. Demonstrating this would require actually finding the defective DNA sequence and proving that everyone with this genotype also had both short fingers and hypertension.

The second issue was variable expressivity, which is a quantitative measurement of the phenotype. In other words, a certain amount of variation could be expected even among those with the phenotype. One affected person might have a blood pressure of 240/130 and another 230/120. That rate might change as a person got older. The same was true of the length of the fingers and other aspects of the skeleton. Even if the syndrome were clearly obvious in a person, such measurements would never be exactly the same.

The situation could especially be confusing in small children; they might have inherited the problem, but it might only be obvious when they reached adolescence or adulthood. Establishing complete penetrance would allow you to develop a genetic test that would accurately predict – even in babies – whether the symptoms would develop later.

"The precise definitions of these concepts was crucial to our work in Turkey," Thomas says. "Every problem in human genetics depends on them. They are somewhat specialized terms, and everyone who went along had to be familiar with them. So before we left, I gave a little crash course for the group."

The exact description of the phenotype and its parameters would become crucial later, as the group happened upon other people in other parts of the world who seemed to have the syndrome. Determining whether that was in fact true would require matching their genotypes and phenotypes to those of the Turkish family.

As Fred carried out his examinations, he anticipated that he might find enlarged hearts and other damage caused by hypertension. But that wasn't the case. Except for the astronomical blood pressure readings, he didn't find anything that you wouldn't expect among a group of people of diverse ages who didn't have hypertension at all.

"Medically speaking, that's a fascinating finding," Fred says, "because it hints that there's something more going on. Something about these people's biology protects them from the normal secondary effects of hypertension. Theoretically, depending on the nature of this protective mechanism, you might be able to switch it on somehow and help people who suffer from essential hypertension for other reasons."

The examinations had another unexpected effect. While listening to the heartbeat of one of the children through his stethoscope, Bilginturan heard a troubling sound. It pointed to a heart defect. It was unrelated to the syndrome, but worrisome enough that the boy needed to be sent to Ankara for further examination. Once he was there, a specialist in child cardiology would recommend surgery.

"That never would have happened if we hadn't directly visited the families," Fred says. "If Bilginturan had done what other groups had asked, and simply driven up there to collect blood samples and send them off to France or wherever, this kind of problem would have gone undetected. It's something you confront as a physician when you're in the field. These aren't just anonymous subjects in a study; they're human beings, and you can't neglect their overall health just because you're interested in some research topic."

In the meantime, Thomas Wienker and Bilginturan were working out the pedigree, with the help of Ali – one of the oldest members of the family. Part of the job was to check the version of the family history Bilginturan had published in 1973 and add members born in the interim. Samples were being collected from the new generation, including the children.

"We interviewed each member of the family, with Hakan or Okan translating," Thomas says. "It took hours and hours, days and days. I didn't have to physically touch them, as the physicians were doing, but many of the questions we were asking were deeply, deeply personal."

It was important to find out whether the women had had miscarriages. "Have you ever had one? Did your mother? How many? At what age?" He also had to ask the women the age at which they experienced their first menstrual period. And this in a culture where men rarely spoke to women at all – married or unmarried – unless a husband, father, or brother was in the vicinity.

"At first this was nearly impossible," Thomas says, "but then Hakan and Okan emphasized how essential it was. And that in Europe there is a protected relationship between doctor and patient, who must be perfectly open about matters of health. Nothing from these interviews would be shared. The brothers did an excellent job, and I have no idea how they managed it. Somehow the family was made to understand that this was a sort of encapsulated environment, that a German medical doctor was allowed to ask an Islamic woman if she had had a miscarriage, and at what age. In the end, we got every bit of information we asked for, to the extent we could present it in an impeccable scientific style. As if we'd done the work in the Black Forest."

After the Toka brothers magically swept the cultural issues out of the way, there remained problems of language – and of memory. "Some normally simple things became incredibly complex," Thomas says. "We couldn't

always tell whether a name that had been written down belonged to a man or a woman. And then we had to find a Latin way to spell it. There was also an issue with birthdays. People usually knew the year they were born in, but one after another told us they had been born on January 1, which seemed like an incredible coincidence. Later we found out that many didn't know the exact day, and when that happened you usually just said January 1."

When did your parents die? How many siblings did your mother have? How many nieces and nephews do you have? "We'd hear something like, 'Yes, I have seven nieces and nephews.' Then you would check that answer against the number of children reported by a person's siblings, and suddenly you had too many nephews. So then you had to go back and interview the first person again."

A few things happened during those discussions that Thomas has remembered ever since. He always carries a pen in his shirt pocket. "A felt tip, the kind with a very thin tip. If I don't have it, I feel naked; I can't think." He was interviewing one of Ali's daughters, a girl of eleven or twelve, and she couldn't stop staring at it. "She was amazed at the very, very thin line you could draw with it," he says.

Finally he gave it to her, a gift. "From the way she reacted, you would have thought it was made of solid gold," he says.

During the first dinner, when the team had outlined their scientific goals to the family, they were careful to explain that the work would not lead to a cure – at least not in the near future. In fact, there was no way to predict whether a cure could ever be found at all. But they might find the cause, and that in itself could be helpful. This puzzled Ali, who had spent long hours having the scientists prod his early memories of lost generations.

"I still don't quite understand why you are going to all of this trouble," he said. "To what end?"

Well, Thomas told him, aside from pure curiosity, the study might make it much easier to diagnose a child with the disease.

This didn't make much sense, either. "Some people can tell whether a baby has it," Ali said. "And if you can't, you can just wait. When he gets older, you'll see."

It was true that after living with the condition for so many generations, the family claimed to be able to tell whether a newborn was affected or not. The scientists hadn't examined any affected infants yet and weren't sure they would be able to repeat the feat. There was no data to show at what age the high blood pressure appeared. Or how early the differences in fingers and toes became apparent.

But that wasn't the point. "If we can find a gene responsible for this," Thomas said, "you might even be able to do a test before a child was born."

What use would that be?

"Well, someone who is sick usually dies when they are forty or so, but sometimes it happens even earlier. Your child might die when he is twenty. If you don't want that to happen, you could terminate the pregnancy."

Ali suddenly realized what Thomas was getting at. He drew himself up and pointed a finger at the physician. "But *you* must die, too. And you don't know when that will happen, either. You might get a disease, or have an accident."

Thomas was startled. "I have personally done hundreds of cases of genetic counseling," he told me later. "But in all that time, I have never been directly addressed in such a philosophical way. It was quite surprising." He

fumbled for words. "Well, there are drugs to take for the hypertension, and it will help you know who should get them."

But it was a weak answer; they both knew it, and Ali shrugged.

Later, when Thomas had time to think about it, he realized that this was his first encounter with a general attitude in the family toward the disease, and it surprised him a great deal. Ali would say that if a person was born with the syndrome, it was simply God's will. That person might live a shorter life than others, but who could judge the value of another life – no matter how long it lasted?

In Germany or other Western cultures, the attitude would likely have been different. Herbert told me, "The discussion about society and stigmatization was fascinating. It's an example of the predictive power of genetics – whether you want it or not, whether based on science or observations from long experience – can also provide a way of living with things. People with the disease are not stigmatized. Even though it's clear when a person has the syndrome, and their family and neighbors know what they might expect, there is no 'us' and 'them'. It doesn't stop someone from marrying an affected person; it doesn't seem to make any difference at all."

Three or four days of asking the same questions over and over, always waiting for a translation, could easily become mind-numbing. Especially when most of the answers simply confirmed what Bilginturan had discovered 20 years ago. But you had to stay alert and follow the protocol with exacting rigor, and be prepared for a surprise at any moment. After moving from the embarrassing to the confusing, to the amusing, the interviews suddenly brought a startling breakthrough on the next-to-last day. Thomas was pushing one of his subjects to identify his grandparents. "Did they have any brothers and sisters?"

From Bilginturan's chart and the information they had gained so far, the answer should have been negative. But the man frowned for a moment and said, "Yes, in fact, there was a sister."

Thomas' sharp felt-tipped pen stuttered across the page. "Do you remember anything about her? We don't have her name written down anywhere here. Did she have any children?"

The man vaguely remembered a daughter – maybe two – who lived near the coast. They had probably married and had children of their own. He hadn't thought of them for a long time. They had a different name.

Simultaneously Thomas, Hakan, and Bilginturan – and the man they were interviewing – realized the same, important thing. This large, extended family had a clan of cousins, and they lived nearby. No one had mentioned them because the families had lost touch three generations ago, to the point that they no longer considered themselves really related.

Thomas hardly dared pose the next question. "Do you know these people? Do they have fingers like yours?"

The man frowned and tried to remember his last contact with them. He wasn't sure.

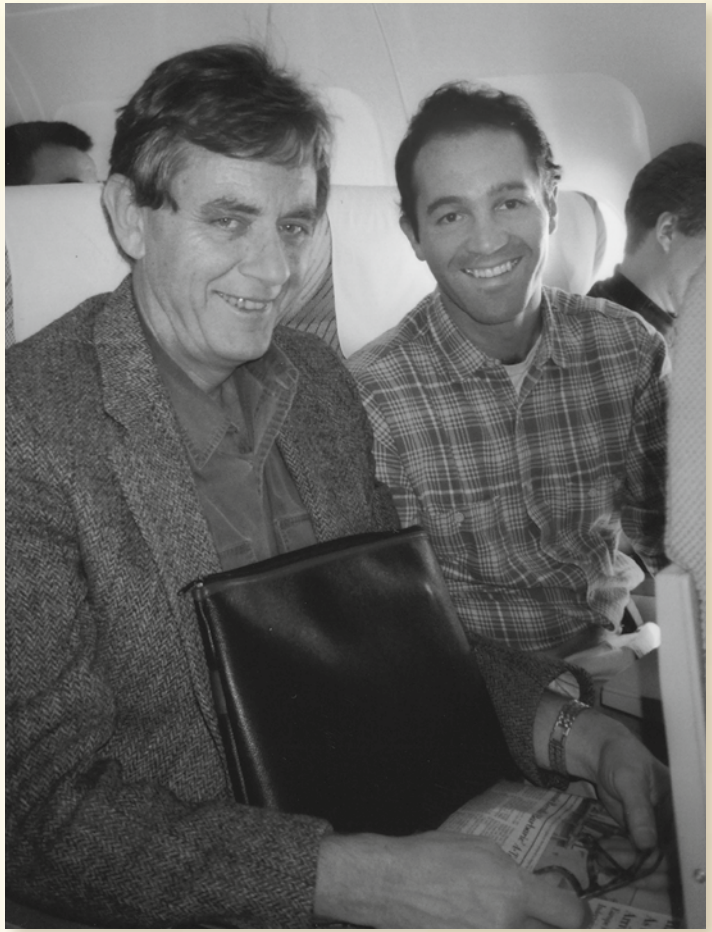
Thomas and Hakan looked at each other. By chance they had discovered an entirely new branch of the pedigree: a group of remote cousins that might, just might, have Bilginturan's syndrome.

But first you had to be sure that the cousins had short fingers and high blood pressure.

Thomas got up quickly and went to find Fred.

For a human geneticist, finding a new branch of the family was the best possible news. Every additional

TheYayla



Fred Luft and Herbert Schuster

family member increased the team's chances of finding the cause of the disease. In fact, finding distant relatives offered the best hope of narrowing the search to a specific gene.

Every birth brings unique new mutations that will be passed along to succeeding generations; every marriage pushes a family's genome farther away from each other. If you wanted to find elements of DNA that were identical in all the affected people, it would be easiest to do against a background that contained as many differences as possible.

Cafer managed to find a phone number for the distant relatives. He made a few calls and returned with a thoughtful look on his face. "We found the sisters, but right now they are up in the mountains, in their Yayla, their summer homes. It's the place we go between the harvests." The scientists knew that the entire village abandoned Karamat for four or five months every summer for a retreat in the mountains. They packed up their belongings, herded the animals together, and made a long trek to primitive summer cottages at an altitude of 1500 meters.

Hakan told me that summers on the coast can get brutally hot, whereas the climate of the high Yayla is cool and dry. "A hundred years ago there was still a lot of malaria on the Black Sea coast, so the mountains were a good place to hide out," he says. "But life up there is very basic. There are no gas lines or electricity, so you have to carry along everything you need."

Now Mehmet told them there were no telephones in the cottages. They would be at home – there was nowhere to go – but there was no guarantee they would cooperate. "And they can't come down. So if you want to meet them, we have to drive up."

"Even by car, it's quite a trip," Cafer warned them, but Mehmet shrugged and offered to serve as chauffeur.

He has often played that role, ever since that first trip; Mehmet drove us around in 2009 as well. When the whole group was on the move, they took the big, rental van. But since only Hakan and Fred would go, Mehmet walked home to get his jeep. The vehicle was at least 15 years old and puffed blue smoke as it mounted the road to Cafer's terrace. The cap for the gas tank had been lost long ago; an old rag had been stuffed in the opening to keep the Diesel fuel from sloshing out.

Another family member, Egemen, offered to go along; apparently, the place wasn't that easy to find. He climbed into the front beside Mehmet while Hakan and Fred took the back seat. As soon as they left the driveway, it was clear that the vehicle didn't seem to have any shock absorbers left. And from the grinding sounds it made when Mehmet shifted, Fred fully expected the transmission to fall out at any minute.

"It was a very adventurous journey," Hakan said. "Several times I thought the jeep would break down. There was nothing you'd call a real road. We drove through streams and over rock formations. When we arrived at the Yayla it was already dark and really cold."

Hakan had only a summer jacket, which he loaned to Fred, who seemed to be freezing. Finally they found a small cabin lit only very dimly by a few gas lamps. Several people were sitting around an old coal oven in the center of the room.

Hakan explained who they were and questioned two of the old women, who turned out to be relatives, and were apparently non-affected. But the women had other relatives named the Domics, who were affected and lived closer to the coast. When Cafer learned of this the next day, he made more calls and convinced them to come to Karamat before the scientists left.

In the hut, Hakan explained what they wanted – fortunately the women agreed to help, because otherwise it would have meant the whole trip had been in vain. But

first Fred announced he needed a bathroom, and Mehmet told him he'd better go along; Fred might get lost.

They were gone so long that Hakan started to get worried. After about ten minutes, they finally returned.

"There is no bathroom," Fred said.

In the meantime their hosts had made tea. Fred held a flashlight and Hakan drew blood. "I couldn't see very well, but somehow I succeeded the first time," he laughs.

They left as soon as they could, facing the same route they had taken during the day, crossing the streams and moving at a snail's pace to avoid big rocks; now the thread-like path had to be found in the deep blackness of night. The trip seemed to take forever. Fred felt giddy; on the way up and down, he discovered, he had been sitting over the partially open gas tank and breathing Diesel fumes.

"I was pretty well anesthetized," he says.

Then Mehmet started to light a cigarette, and Fred's eyes grew round. "*Not* a very good idea," he said. "I wasn't *that* far out of it. Under the circumstances, lighting a spark wasn't a great idea." He yelled at Hakan, who told Mehmet to put his lighter away, *fast*.

Their adventures for the night weren't over yet. Halfway down they saw the glimmer of a fire and the trail was blocked by a group of men with rifles slung over their shoulders. Mehmet stopped the car and spoke to them. Somehow the men had heard that a group of "German Professors" were lost in the Yayla.

"They're 'inviting' us for a snack at their bonfire," Hakan explained, after a long conversation. "Mehmet tells me it's not a very good idea to refuse."

Fred was exhausted and would have preferred to move on, but he sighed and opened the door. At least it would provide a break from the fumes. He sat close to the bonfire the men had built and tried to soak up a bit of warmth. They stayed just long enough to eat a few baked potatoes they were offered, prepared over the fire, and were back on their way 20 minutes later.

Finally they reached Karamat and its gravel roads – rough, but an infinite improvement – and aimed for their hotel on the coast. They arrived at 4am and fell into bed, utterly exhausted.

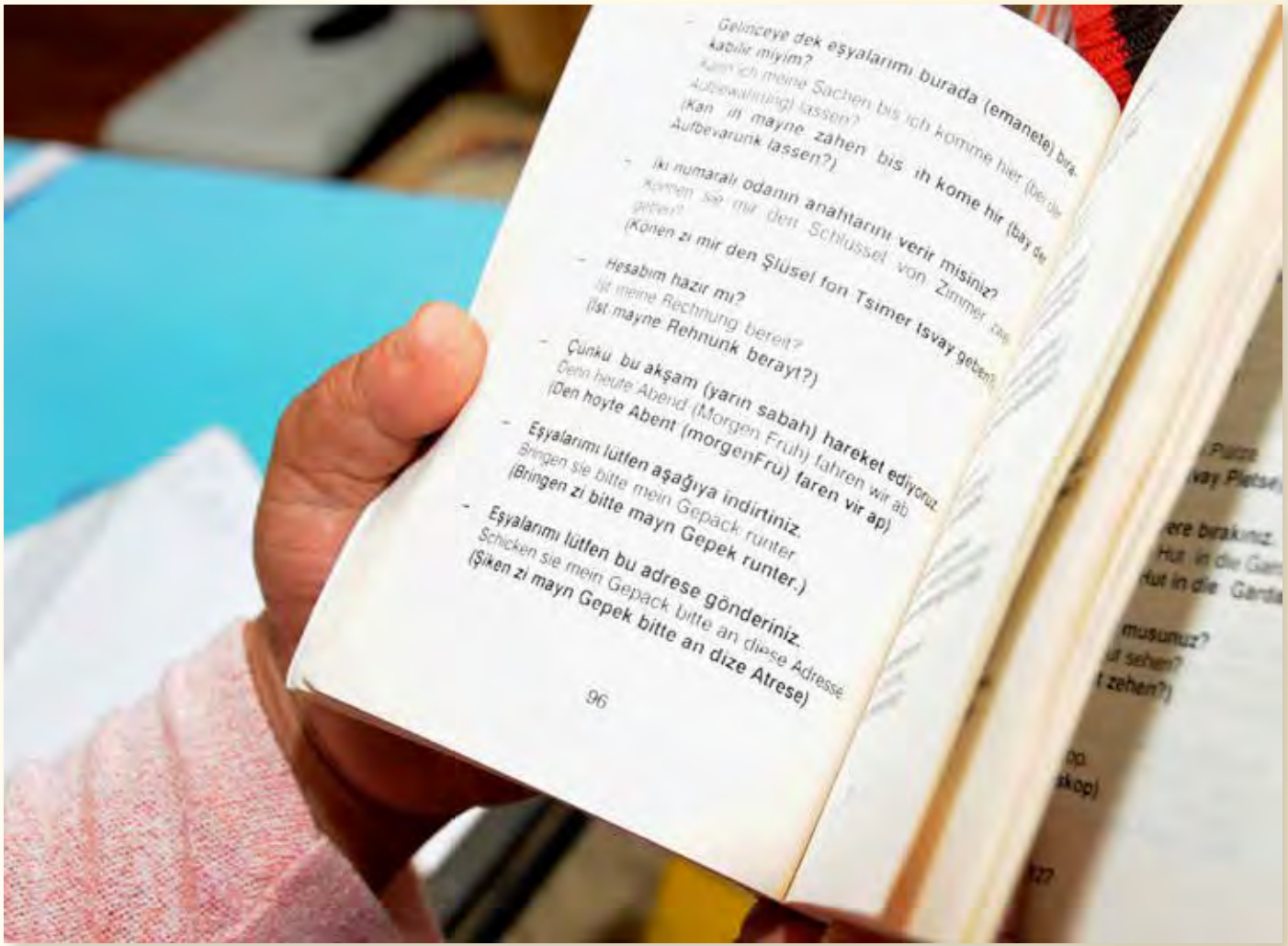
But the next day a few other members of the new branch of the family arrived. They were nieces and nephews of the two women in Yayla and were clearly affected, which meant taking more blood and blood pressure measurements.

Their interviews with Thomas put more flesh on the bones of the pedigree. And they yielded one more extremely important fact: one of these distant relatives, a carrier of the syndrome, had moved to Germany. They lived in the city of Stuttgart, several hundred kilometers from Berlin, but much closer to the researchers' home than Kamarat. The family provided an address.

Now the disease could be directly studied in Germany as well, with family members that spoke the language. Now, many years later, one member of that transplanted family may turn out to play a central role in understanding the genetics of hypertension.

After a week of investigations, the scientists were exhausted but exhilarated, and Cafer's family was clearly exhausted – it had been difficult keeping two infant children out of the scientific gear scattered around the house. The team began the process of packing up, preparing the blood for travel, and helping clean up.

The last evening brought a final dinner with members of the village whom they had come to know to a very rare and particular degree of intimacy. All of them would find it hard to part ways. The language barrier


- Gelinceye dek eşyalarımı burada (emanete) bıra-
kabilir miyim?
Kann ich meine Sachen bis ich komme hier (bei der
Aufbewahrung) lassen?
(Kan ıh mayne zahen bis ıch kome hir (bay der
Aufbevarunk lassen?)

- İki numaralı odanın anahtarını verir misiniz?
Können Sie mir den Schlüssel von Zimmer zwei
geben?
(Können zi mir den Şlüsel fon Tsimer tsvay geben?)

- Hesabım hazır mı?
Ist meine Rechnung bereit?
(Ist mayne Rehnunk berayt?)

- Çünkü bu akşam (yarın sabah) hareket ediyoruz.
Denn heute Abend (Morgen Früh) fahren wir ab
(Den hoyte Abent (morgenFru) faren vir ap)

- Eşyalarımı lütfen aşağıya indirtiniz.
Bringen sie bitte mein Gepäck runter
(Bringen zi bitte mayn Gepek runter.)

- Eşyalarımı lütfen bu adrese gönderiniz.
Schicken sie mein Gepäck bitte an diese Adresse
(Şiken zi mayn Gepek bitte an dize Atrese)

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was still there, but somehow it had become barely noticeable. The family and scientists sat together on the ground on Cafer's large terrace. Everyone was talking and laughing. Someone had arranged for music – a live band – and there were a few attempts to teach the scientists the words to songs. Of course they fumbled with the words, and of course each attempt provoked new heights of hilarity. Bilginturan had sung along; the distance of those first days had dissolved, and he laughed at them, too.

So they gave up on the songs, and ate for a while, and then Hakan said, "Did you hear what happened to Fred?"

No, they hadn't.

He told them about the diesel fumes, and they found this highly entertaining. "It sure made me wish I knew a few words of Turkish," Fred said. "Like, *STOP*."

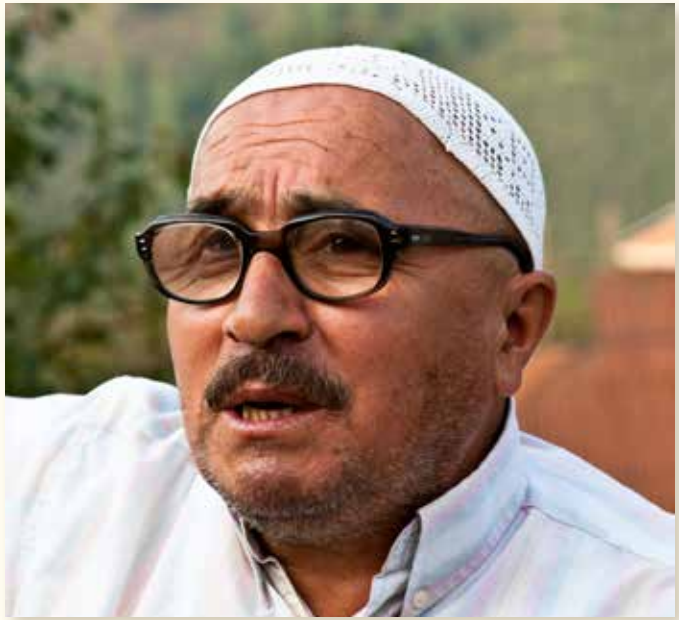
Ali leaned forward and said, "If you really want to know us, you'll have to hear our jokes. Nobody can tell jokes like the people in Karamat."

"It's because there's nothing else to do," someone said.

Hakan told Fred, "I think they're challenging us to a duel."

With little other form of entertainment, the family told little jokes about themselves, usually infused with a healthy dose of self-irony. You find that in small towns across the globe. Since everybody knows what everybody else is doing – or will very soon – information becomes a mode of exchange; gossip is honed to a fine art. And in Karamat, everyone was related in some way or other, which created the best possible breeding ground for stories.

Now Ali launched into one. Jokes are devilishly hard to translate, because timing is everything, but Hakan did his best. "A farmer from a nearby village was at a soccer match in a large stadium…" Ali began. (Pause for translation.)



"That's an old joke," someone said.

Ali glared and started again. "A farmer from a nearby village was at a soccer match, and he looked out across the field, and suddenly in the stands on the other side he saw one of his friends. 'Hey Mehmet!' he called."

"Why did you call him Mehmet?" said the real Mehmet, who was sitting across the table. It earned him the next glare.

"'Hey, Mehmet!' he called," Ali continued. "Of course Mehmet couldn't hear him. So he yelled even louder, 'Mehmet, Mehmet, why aren't you answering me?'" Ali cupped his hands to his mouth and yelled, at a startling volume that might not cross a soccer stadium, but they heard him for sure in the next village.

As he replayed the line in English, Okan cupped hands to his own mouth, which highly amused the hosts. The translation was quieter, and one of the women suddenly cried, "Louder, louder! We can't hear you!"

That made them all laugh. Ali glared some more before continuing: "So a man sitting beside the farmer said, 'Who are you talking to, and why are you shouting?' 'Well, that's my friend Mehmet over there, and he can't hear me.' So the man next to him gives him the binoculars he has brought along to watch the match and says, 'Try these.' The first one takes them, puts them up to his eyes –" Ali pantomimes. "He looks through them, and now his friend appears very close. He's looking through the binoculars and now he says, in a normal speaking voice, 'Hey Mehmet! I've been calling you! Why don't you answer?'"

Yes, it was an old joke, but the Turkish family laughed uproariously. Okan began to laugh, and it infected the scientists even though he hadn't reached the punch line yet.

"I don't think that's very funny," Mehmet said. One of the women had a high soprano giggle that soared an octave above anyone else's, and Mehmet's pronouncement made her laugh again. She couldn't stop, which they found hilarious, so that went on for a while.

Well now Mehmet had to tell a story, of course, and he began, "Did you hear what happened to Musa's car?"

"Don't tell that story!" Egemen, who was sitting next to him, wanted to say. But his mouth was full and food went down his windpipe, which made him cough. The man sitting next to him pounded him on the back with such force that Egemen's small cap threatened to fall off. He put up his hands to hold it in place. Another blow to the back and one of the buttons of his shirt popped off, like a little bullet, shooting off and bouncing across the terrace.

The woman with the high giggle lost it again, and they all laughed. Hakan, who was translating this time, wondered if they'd ever get to the point.

"Musa was driving up in the mountains, and he took a wrong turn," Mehmet said.

"I didn't take a wrong turn," Musa protested. "You think I don't know the way to my own house?"

"He was up in the mountains on this very narrow road, and he had to turn around," Mehmet started again.

"*Don't* tell that story," Egemen said again, with such violence that the scientists thought a fight was about to break out. His protests brought on the giggle again, and another general state of pandemonium. Even the scientists laughed, although they had no idea what was going on.

"But the story's *true*," Musa said. "And remember what Dr. Wienker said: we had to be completely honest. Don't worry, it's *private*, he won't repeat it in Germany."

More high shrieks from the audience. Egemen's face was darkening.

Fred said, "Do you think we're ever going to get to the end of this story?"

Finally things got back on track. "Musa had a big car, and he had to turn it around on a tight road," Mehmet said, dutifully translated by Hakan. "A very narrow road. Narrower than the car. So he drove forward and back, forward and back, and finally he told his friend Egemen to climb out to give him directions. 'Go left,' Egemen called. 'No, wait! Go right! Left – right – left.' Then at one point he gets the directions confused –"

"I didn't get confused!" said Egemen, whose face was getting even redder. "Musa heard me wrong."

"– He got the directions confused and said 'right' when he should have said 'left'."

"It was the other way around," Musa said.

Mehmet glared at him. "So the car goes over the side of the road and drops a ways, maybe two meters –"

"One meter," Egemen said. "Maybe not even that. It was just a little bump."

Mehmet kept pushing the story along, and Hakan continued translating, Egemen protesting all the while. "The car crashed, and it was totaled. Fortunately Musa was okay. He was okay enough to get out, and get mad, and here he comes running towards Egemen."

"I thought he was going to hit me," Egemen said. "You know how he gets."

"So Musa said, 'What's the matter with you, can't you tell left from right?' And Egemen said, 'What's wrong with you, why are you so angry? *It was an old car anyway*!'"

Screams of laughter that went on and on. Egemen scowled. "It really *was* an old car," he mumbled.

"It may have been old," Musa said, "but it was a *good* car." He was laughing as hard as the rest.

"A *very* old car," Egemen said, unable to keep from giggling himself. "A piece of *junk*."

"*Well, it certainly is now*," Musa roared.

And everyone completely lost it; every time Hakan tried to translate the last line he broke down, and Okan tried to translate it and laughed even harder. Tears ran down their eyes, and when one of them finally got Musa's words into English, the scientists laughed so hard that it set everyone off again. By this time, of course, Egemen and Musa were so out of control that no sounds emerged from their mouths; Egemen just held his sides and shook up and down.

Then darkness fell; on the side of the terrace that faced the Black Sea, long pastel stripes spanned the climes of the sky. The men lit a fire and a lantern that hung from the eaves of the barn. And this evening outside, with its fine, balmy breeze, would always remain in the visitors' minds.

No wonder Bilginturan had been stiff at the beginning of the trip, Fred thought. How ludicrous and callous it would have been to ask him to just drive up here, draw some blood, and FedEx it out of the country – as the groups in France and England had done. Bilginturan hadn't been thinking of his prestige; he'd been thinking of his patients. He'd seen them as real, human beings who were willing to do almost anything you asked, if you treated them honestly and with respect.

Fred would remember this feeling for many years; it would sustain him whenever the project slowed down or seemed to hit an impasse. There might be political or financial reasons to drop the project, but in doing so you'd also be abandoning human beings. The many scientific papers that would emerge from this work might fly high overhead in some abstract, intellectual sphere, but you should never forget that they were ultimately tethered to real people who stood firmly on the ground.

Could a research project have any better birth? In a few short hours they would be gone, this strange mix of Germans, a German-American, a Turkish physician, two young Turkish-Germans. Sure, they'd be taking along data and charts and dozens of tubes of blood. But wasn't this a much richer thing to be taking away? A memory of a song you couldn't sing, of jokes and laughter, and of a feast prepared in friendship, by small and gracious hands?

Sylvia Bähring

11 Digging into the foundations

Herbert and Hakan had been gone for a week. Sylvia Bähring had stayed behind in Berlin – somebody had to run Herbert's new lab – and was experiencing a bit of an adrenaline rush, waiting for their return. She knew they would be bringing back blood, and every single sample was crucial to the success of the study. But her only experience in extracting DNA came from cell lines; blood was another thing entirely. Nowadays there is a kit, a standard procedure that is fairly routine, but in 1994 the process was a lot harder. It was easy to get wrong and ruin a sample that could never be retrieved.

Actually her adrenaline had been cresting a lot longer. The six months since she'd joined the lab had been marked by periods of total chaos. In April, for example, she had seen the space allocated to Herbert's group for the first time. Sylvia, her colleague Evi Jeschke, and an architect had the job of converting the room into a modern lab. But at the moment it was just an old office in the basement of the Franz-Volhard Clinic.

The custodian found a key and opened the door and she immediately thought, "No. Impossible. *Never*." Somebody had been using the space to store boxes of junk. There weren't many of them, but they were enough to fill the room. Sylvia and the custodian carried

everything out in the hall. With a filling of pure dread she measured the room.

Something else was bothering her, and it took her a moment to figure it out. Nobody had bothered to measure the room's height. The ceiling already seemed low, and that wasn't counting any ventilation ducts they might need to install. It might do if you could find scientific equipment – and scientists – built to the scale of short-fingered Turkish farmers, but she doubted that many biotech companies had been targeting that particular niche in the market.

"The ceiling is way too low," she told Evi, who went off in search of Herbert. He came and had a look, and then went to find Fred. A few minutes later they were all standing at the door scratching their heads.

"Can't very well raise the ceiling," Fred remarked. He scuffed at the floor. "I wonder what's under here?"

They dragged down a workman who scrounged up some tools and began, after a considerable amount of persuasion, a small excavation in one corner. What was under there, it turned out, were a bunch of layers of stuff. He summoned another workman. More scratching of heads.

Under the floor were layers of other floors and concrete that could, theoretically, be removed. More head scratching. The final verdict: if you were willing to saw through the top layers and attack it some more with pickaxes and raise a hell of a lot of dust, you could add twenty centimeters to the height – well, the depth – of the room. It would create a step down going in and a step up as you came out, which meant they would stumble over the threshold a lot until they got used to it. I visited that room twelve years later, after they had moved to another building and acquired ten rooms the size of this one and foisted the space onto another group. I tripped on my way in.

As the work got underway, Sylvia and Evi began ordering equipment. In between the orders, they made drawing after drawing on graph paper to find a way to cram everything into this tiny space. When they got stuck they called the architect. At one point they had it all figured out.

A scientist didn't spend all of his time at the lab bench, or running a machine; it was equally essential to have an office where you could write up your results, write grants to gather in all that money lying on the street that Detlev Ganten talked about all the time, and maybe, once in a while, to think. Or just to take a break.

Those functions would be filled by a second room next door, a much smaller one, which they'd all have to share. Sylvia had never dared measure it; later the architect told her it was ten meters square, smaller than her childhood bedroom. And all of them had to fit in there. Everyone had a space to sit, if you held perfectly still and didn't move more than a centimeter in any direction. You'd never be able to sit back-to-back at opposing desks. The room doubled as a break room, which was fine if nobody had any real work to do and half the group had gone outside to smoke.

By September 1994 – just two weeks before the trip to Karamat – the rooms were finished. Most of the machines had arrived and been installed. The group threw a "housewarming" party in the new lab amongst their sparkling new machines. There wouldn't have been enough space in the office. Any time someone came in or left, Sylvia said, "Watch your step."

Herbert's group now had five members, counting himself. Sylvia immediately started operations in the lab, with a young female assistant working on her undergraduate degree. Then one day a man named "Mr. Zhou" appeared on their doorstep with practically no warning. Detlev Ganten had hired him within the framework of a new partnership between the MDC and a university in China. By some decision-making process that none of them

Hakan and Evi Jeschke

completely understood, Detlev decided that Mr. Zhou should join Herbert's lab. Things would have worked out better if the new colleague had spoken any English at all. But communication was nearly impossible.

"He was nice," Sylvia says, "but every time we went to lunch together, or ate in the office, he made these incredible, loud, horrible, disgusting slurping sounds that seemed to last for minutes." Atakan, who was there when she said it, tried to imitate it. "Stop that!" she yelled. Old wounds run deep.

Later she learned that in China, this behavior belonged as much at the dinner table as knives and forks in Germany. It showed appreciation for the food, a way of complimenting the host. "We never got used to it," she says. "I just kept hoping we'd never be sent to China as part of the exchange."

During that period Hakan had had no time for research; he was completely occupied with preparations for the trip. "I'd tell you he had everything spread out in the office, if but there wasn't enough room for it to spread out," Sylvia says. "Let's say it was all 'deposited' in there. And he hogged the computer all the time. We only had one, and the rest of us needed it, too."

The situation led to a clash between Hakan and Evi Jeschke, who had been hired as a manager for the new lab. "She's a – well, let's say 'strong-willed' native of Bavaria," Sylvia says. "That was great at the time, because we needed someone who could make very firm deals about our equipment with representatives of biotech companies, and also with all the workmen trying to get the lab ready."

"Everybody in the lab was sort of terrified of her," Hakan says. "I was under a lot of stress because of time constraints, so I had stuff for the trip in the lab and the office, pretty much all over the place. She didn't think it belonged there – it was in the way, and she needed the computer to work on the hypercholesterolemia project Herbert had brought along from Munich. I guess she thought, 'Here's this egotistical medical student from Munich who thinks he can hog all the space.' The reality was that I was completely stressed out and had nowhere else to put all this stuff."

The group was still getting to know each other, and would have to work together for a several years; here, in the first few weeks, they were already getting off on the wrong foot. Sylvia and Hannelore Kretschmer, a technical assistant with a calm personality, tried to keep things diplomatic. But things were reaching the boiling point and Hakan had to get creative to smooth things over.

He consulted with a Greek friend named Leonidas, his next-door neighbor in the campus guest house; when it came to situations with women, Hakan discovered, Leonidas had a great deal of experience and was the person to go to.

"It's simple," Leonidas said. "You're in her space. She wants attention, and you're not giving her any. It's almost as if she came home and found you working in her kitchen without asking permission."

The solution, Leonidas said, would be to take her out to dinner. "She'll be flattered and feel like she's back in control."

Hakan was skeptical, but Leonidas was the expert. He approached Evi and asked her out to dinner with a lame excuse: He needed to discuss an important lab matter with her.

"I could tell she was suspicious about my motives, but she told me that in three days she'd have time for a quick snack on her way home from work." Over those next three days, he noticed that her attitude had softened; she didn't get as upset with him.

On the big day he followed her in his car into the city, half-way to the home where she lived with her fiancé. They stopped at a Greek restaurant, went inside, sat

down, and peered at each other over the candles on the table.

"All right, Hakan," she said straight out. "What's really going on?"

"I'd laid out a plan with Leonidas. Basically, I wanted to tell her I was under a lot of stress and appreciated her for putting up with all my recent activities in the lab. But I was totally surprised that she just came out and asked me so directly – I knew what she was thinking, and I didn't know what to say. I stuttered and tried to think of a good reason – well, a different good reason – why I might have asked her out."

His discomfort made Evi smile. "It's all right, Hakan," she told him nicely, "I like you, too – as a friend!"

She had misinterpreted his intentions, thinking he was "interested" in her, but he could live with it if that's what it took to break the ice and smooth over the tensions in the group. The dinner ended on a pleasant note. Hakan realized he now owed Leonidas a dinner, too.

Starting at that point, Evi greeted Hakan with a smile when he entered the lab in the morning, and he could sit at the computer as long as he needed to. A year later she even invited him to her wedding where, he says, "I honored the bride and groom with a Bavarian folk dance I had learned as a child in Munich."

I think he told me that for the performance he put on "Lederhosen," the traditional short leather pants worn in Bavaria on such occasions. But mysteriously, photographs of the event seem to have disappeared.

So the group's departure came after a long period that was "a bit chaotic," Sylvia says, but things were back on the right track. When the group left, they took all of Hakan's "deposits", the computer was free again, and the members of the team could enjoy a week in their office in which they weren't constantly playing bumper cars with the chairs.

In Turkey Fred Luft had been putting together a more concrete plan for the next steps in studying the family's health. The long-term goal, in the hands of Herbert, Thomas, and Sylvia, was to find what they suspected was a variation in a gene. An even longer-term goal, which the researchers might not see in their lifetimes, was to find a cure. It was a bit like setting off from Karamat toward some distant coast, without really being sure it existed, or that the path you were taking wouldn't run into a dead end.

Fred's role at this point was to develop a research program that could be broken down into manageable pieces and had a realistic chance of success. But another issue, the family's health, was crying out to the physician in him. And dealing with that would require taking several practical steps, almost immediately.

Few of the short-fingered subjects in Turkey had health insurance; those that did had been to doctors and been prescribed drugs to address their high blood pressure. He could tell from the week's measurements that the treatments weren't having much of an impact. Ali and several of his affected relatives were and Ali and several of their affected relatives were reaching a critical age; if they weren't treated, many of them would die, and it would probably be soon. Fred's top priority was going to be simply saving their lives. The way to go about it would be to carry out a thorough trial with existing drugs, hoping to find one that would bring the hypertension down to reasonable levels, and the sooner the better. Ali and Cafer had promised to discuss the idea with the families.

Fred knew that such a study would be a long, hard job that would probably require somebody to put his life on hold for the better part of the year. The alternative would be to find somebody in Turkey to do it, but Nihat Bilginturan advised against it: he didn't know anyone who'd be

willing or motivated enough to get it right. "It's better to send someone over," he said, "and it must be someone who speaks Turkish. Like one of those young men over there." He pointed at the Toka brothers.

They project would also require a much deeper look at the family's symptoms than had been possible in Turkey. The team needed much stronger proof that they were dealing with a form of essential hypertension before the drug study began. That would require a range of tests that had to be done in a hospital, and Fred couldn't even begin to imagine the nightmare of red tape required to carry them out in Trabzon. Better to bring a few family members to Berlin, and to do it soon.

And it was important that the family seemed to be free of the collateral damage that usually accompanied hypertension. A careful examination in the hospital might reveal unusual features of their organs or blood vessels that could be useful in treating other hypertension patients. The features might also help zoom in on weak points in the body that raised blood pressure in the first place; currently, scientists didn't know where to look.

Peter Jannetta and Ramin Naraghi had proposed that the brain might be the source of the problem, or at least part of the solution. Fred wasn't yet convinced that the cause was a nerve pinched by a blood vessel – there wasn't enough data – but his experiences in Erlangen had come to mind several times during the week. At some point he ought to call Ramin.

And they should have a look at the family in Stuttgart as soon as possible.

They touched down in Germany with the 60 or so blood samples that had been drawn from the arms of remarkably patient farmers and their brave children, who had fought back tears or openly cried at the approach of the needle. Now the task was to examine the DNA in that blood to find what was probably a defective gene.

That was likely to be a very long haul. Today when a scientist travels this route, he faces the scientific equivalent of the modern highway along the southern coast of the Black Sea; high-throughput machines race down it at an incredible place. Even now it can take a long time to reach your destination, especially if it lies in a tiny region of human DNA for which there is no high-resolution map; when you get close, the signposts might disappear.

But in 1994, the road had barely been marked out and was full of gaps that sometimes couldn't be leapt over. It often ended at a technical brick wall. All you could do was set off at a snail's pace and hope you arrived – somewhere, someday.

Sylvia Bähring hadn't yet visited the roads of Karamat, but she was intimately familiar with the scientific equivalent. "Nature is more complex than any doctoral student can imagine, and you often run into unexpected problems," she says. That wasn't always a bad thing; if you were willing to keep butting your head against the wall, sometimes you would break through to a new and interesting place.

It helped if you were accompanied by someone who seemed fearless, who could inspire you to keep trying, and in that regard Sylvia had been lucky many times. Sinaida Rosenthal, the head of her first lab, had been like that – until her untimely death left the group in a state of shock. At that point the lab was taken over by Michael Strauss, whom she calls an "unshakable optimist."

Strauss was a virologist whose group focused on a virus called SV-40. When German reunification came in 1990, he took the opportunity to shift his focus to cell cycle regulation and gene substitution, topics that would survive the scrutiny of a review panel from the West. The key to obtaining funding was to produce results. That didn't mean Strauss had to come up with a miracle cure,

but his research would need to produce findings that the scientific community deemed important. Strauss eagerly made the transition, and his group was integrated into the Humboldt University of Berlin.

"He was totally engaged in integrating his group into the new research landscape," Sylvia says. "We all owed him a lot as both a scientist and a person, and his early death in 1999 was a great loss to us all."

The lab began working on developing a system based on liver cells that could be raised in the lab and used in attempts at "gene therapies" – a method to deliver healthy genetic information to the cells and body systems of a person suffering from a genetic disease.

For Sylvia, it was a perfect opportunity to learn a whole range of biotechnological methods. She was now 29 years old, was getting familiar with lots of technology and becoming remarkably adaptable to change. For someone who was about to work with Herbert Schuster and Fred Luft, those were good characteristics to have.

Her doctoral degree in 1994 armed her with the title "Dr.", and she decided to take matters into her own hands. "I felt like I had enough technologies under my belt, at least for the time being, and that I wanted to do more than just molecular biology," Sylvia says. "Beginning your postdoc is maybe your last chance to really consider what you want to do and make a significant change. I talked to Michael Strauss and several people and thought a lot and in the end, I decided to go back to a theme in school that had inspired me to go into science in the first place."

The school system in the East put pressure on pupils to commit to their future careers early; "It started in the eighth grade and got more intense after that," she says. "I didn't really know what to do and I resented it a bit that I had to decide. Choosing a lifetime career is not the uppermost thing on most teenagers' minds."

But interesting classes and an extracurricular club in biology started to pull her in that direction. The group did a lot of things she found fun. "Under the microscope we looked at bacteria and thinly-sliced preparations from plants that we'd made, and learned a lot in a really stimulating way."

Of all the topics they covered, Sylvia found heredity the most interesting – especially human genetics. She learned to work out pedigrees; she heard about research into the functions of genes, and learned that the mutation of a single letter out of the three billion bases that make up the human genetic code could lead to serious human diseases.

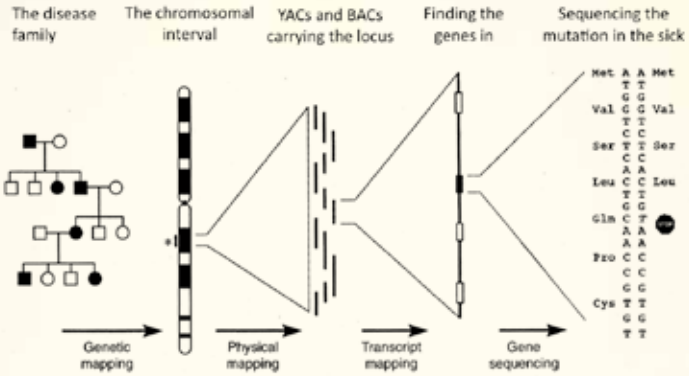
She was trying to decide where to apply when Herbert Schuster arrived to give a talk about his work on genetic diseases involving the way the body processes cholesterol. Sylvia thought, *That's it, this is what I want to do.* But where, and in whose lab?

Shortly after that, when Herbert was hired by the MDC, the timing couldn't have been more perfect. When Herbert received her application, he remembered her and hired her to run the new lab. It was another thing she hadn't done before, but Sylvia was eager to get started. First, though, some practical issues had to be dealt with – like digging up the floors.

Sylvia tried and tried to explain how the group discovered the location of the defective DNA that caused Bilginturan's syndrome, using an approach called *linkage analysis*. Although I understood every word she said, I still wasn't getting it. She was butting against another wall, but this one was in my head.

Often this happens because scientists know things that are so fundamental to their work that they almost never talk about them, rarely consciously think of them, and

The path from a disease to its genetic cause



don't realize that a non-scientist like me doesn't know them. To solve the problem you have to flush such ideas out into the open. You could surely explain to somebody from the 15th century how to get from Paris to Berlin by traveling west, for example – but it would be hard if you forgot to tell him that the world is round.

I was getting stuck because I kept thinking about genes, and at this point in the research, genes were almost completely irrelevant. What Sylvia, Herbert Schuster and Thomas Wienker had to do was pin down the location of the problem to a region in one of the 46 human chromosomes. In most cells chromosomes come in 23 pairs. Each is similar, but not identical, to its partner – with the exception of the 23rd pair.

Why do some parts of my face look more like my father, and other parts more like my mother? It's actually a wider effect that happens all over my body and in each of my cells. The answer has at several parts. First, pairs of chromosomes usually bear the same genes, in slightly different forms: the alleles. One of these. One of these is usually dominant – it determines how the cell uses it to produce proteins.

But chromosomes are not inherited as units from a person's parents. Each egg and sperm receives a half set of DNA – one of each of the pairs. These originate, however, from cells that have full sets of pairs. As reproductive cells form, the pairs of chromosomes of a parent line up and intermingle. If you think of a chromosome as one of those nest-like bundles of tagliatelle noodles, it's easier to understand what happens next. In the bag, the strands of different "nests" often become ensnarled, and some of them might break as you pull them apart. For its scale, DNA is fairly stiff – more the consistency of a noodle than of yarn – and stress causes the strand to break.

A cell can usually fix this problem: repair molecules normally determine where the pieces have come from and insert them back into the strand. The breaks can happen anywhere – in the middle of a single gene or in the space between different ones. They can also separate a gene from sequences that help switch it on and off, the operons discovered by Jacques Monod and François Jacob.

However, the repair system doesn't always work. It might reinsert fragments of chromosomes in the wrong way, or the wrong place. A piece originally from one chromosome of a pair might be plugged into the other, giving the target chromosome two copies of the fragment and the other none. Or pieces from the two strands might be swapped. Or a fragment might be inserted backwards. And if things really go wrong, it might be installed in a completely different chromosome in a process called *translocation*.

Any of these mistakes might give a chromosome a new structure that has an effect on genes, because a fragment may be large enough to contain dozens of them. The break might separate a gene into two pieces that can no longer function. Or a gene might move away from sequences which formerly ensured that it was only switched on in

the right tissues at the right times. Any of these problems can cause a serious genetic disease.

All of these *recombination* events are crucial in a human genetic study because they create changes in the size and locations of specific sequences in a chromosome. Those shifts are sometimes the only landmarks a scientist has in trying to find the location of the genetic defect at the heart of a disease.

The only thing that Fred's team knew when they started their study was that the syndrome of hypertension and short fingers followed a monogenic pattern through the generations of the family of Karamat. The pedigree they obtained during their trip sharpened the pattern from Bilginturan's original study. It confirmed who had the disease and who didn't, and whether he had inherited it from his mother or father.

With this information, they had to identify a specific region of a chromosome which was present in a particular form every single person with the disease, but found in a different form in all the healthy family members. It wasn't really like looking for a needle in a haystack. It was more like looking for a few specific needles in a needle factory.

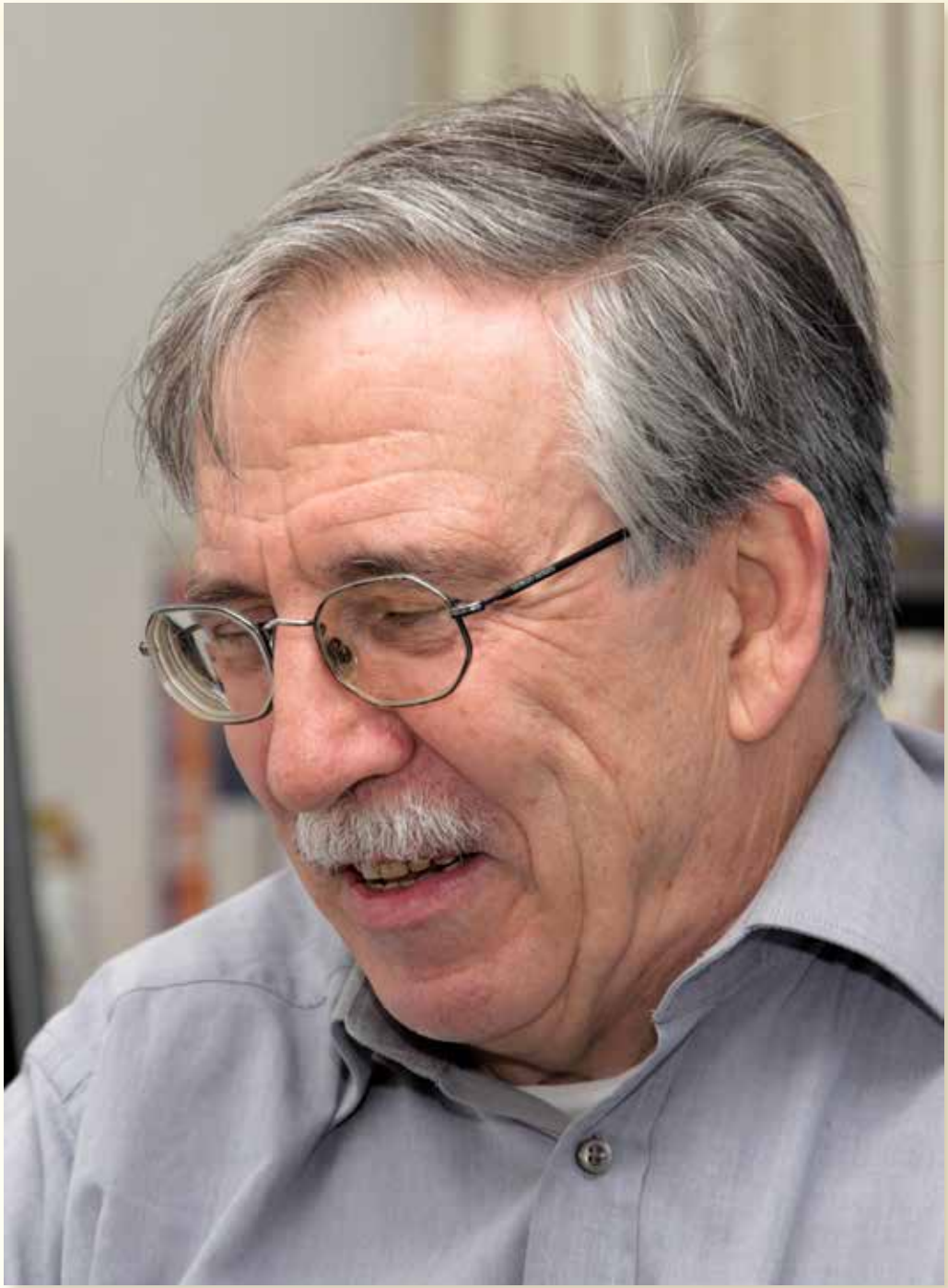
The first step was to extract DNA from the blood, which Sylvia's colleagues managed, despite her initial concerns. Now they had to study that DNA using a new technology that was still being developed by the biotech industry and had yet to become commonplace in most research labs.

This new method was tightly linked to a discovery made by researcher Alec Jeffreys at the University of Leicester, in the UK, in the 1980s. His work revolved around the amount of variation in the human genome – in other words, how much your DNA differs from that of your parents, close relatives, and every other human being on the planet. What he discovered led to the invention of an application called *DNA fingerprinting*, which is now featured in practically every crime show on television. The method allows you to find unique features in a DNA sample and match it to another sample with incredible accuracy. So if you have DNA from a person's cells, you can definitively determine whether he left a particular trace at a crime scene. The procedure is commonly used as evidence for the guilt of a suspect, or to free someone who has been wrongly accused of a crime.

Studies had shown that changes in DNA happen all the time and that every gene can be found in many varieties in a population. Even if you've inherited a complete gene from one of your parents, there will be a variation on the average of one in every 1,000 letters of the sequence. These tiny variations in particular regions led Alec Jeffreys to develop a way of comparing very similar DNA samples in search of small changes.

In 2006 I met Jeffreys in Heidelberg, and he told me a story he had repeated many times. In the 1970s he was using proteins called *restriction enzymes* to chop up the DNA he had obtained from human cells. These enzymes work by docking onto specific sequences in the genetic code and breaking it, leaving small fragments that were much easier to study than complete strands of DNA. You could, for example, compare the fragments obtained from different people. But the enzymes could only do this at exact combinations of letters. So, for example, if you had a variation somewhere in that string, a restriction enzyme couldn't make the cut. If your mother didn't have that variation, your fragment would be a different size than hers, and this could be measured in an experiment.

Variations in these specific sites don't happen very often, however, so in most cases you and your mother are likely to end up with fragments of the same length. Jeffreys wanted a way of comparing the actual spelling



Thomas Wienker

that made up each sample. The big breakthrough came in September, 1984, and it occurred because Jeffreys found multi-lettered regions of DNA that change a much higher rate. So much so that about one in four of us acquired or lost extra repeats as we inherited DNA from our parents.

These highly variable regions, called *microsatellites*, are composed of repeated clusters of just a few letters in the DNA sequence. They usually occur outside of genes, in segments of the genome that don't encode proteins. Not only are human chromosomes littered with microsatellites, Jeffreys found a way to see them. He found a pattern common to many of them and developed a probe that could dock onto regions that contained specific numbers of copies. If now you exposed the fragments to X-rays, the microsatellites would appear as dark stripes. If a sequence had the right number of repeats to attract a particular probe, you would see a stripe at that position. If it had fewer repeats, there would be no docking and no signal from the probe.

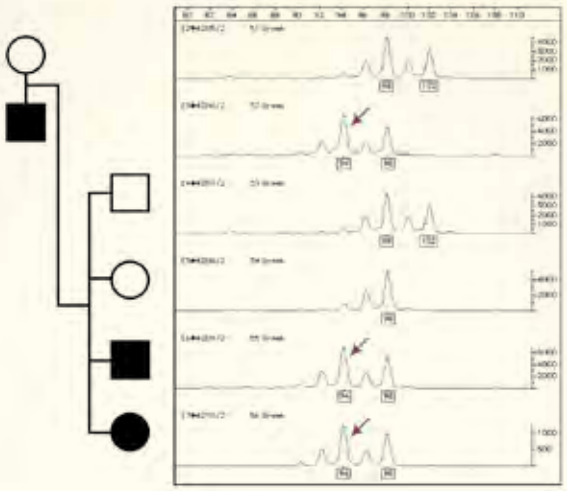
By chance, the first samples Jeffreys loaded into his machine included DNA from one of his technicians and each of the young individual's parents. Each person's sample had unique stripes, which meant that the microsatellites could change at an unexpectedly high rate. It was high enough, for example, that your two parents would have a lot of different ones, even if they were distantly related. Half of the unique signature from each parent would be passed along to each child. By comparing markers in the technician's fragments to those from the parents, Jeffreys could tell whether every bit of DNA in his chromosomes had come from the mother or father.

He instantly realized the immense potential uses. You could match a DNA sample to a unique individual, making it just as valuable as real fingerprints in the investigation of crimes. You could also resolve questions about paternity by matching the sample from a child to a parent. Thanks to the discovery, a lot of intriguing mysteries have been cleared from the books: The remains of a body found in Brazil were truly those of the long-hunted German war criminal, Josef Mengele. The entire family of Tsar Nicholas Romanov II was indeed murdered in 1918, as Russia underwent a revolution – despite legends that some of the victims had survived. And yes, the outlaw Jesse James was killed in 1882.

Putting DNA patterns from crime scenes or convicted felons into databases has led to coincidental matches that wouldn't have been obtained through other means. In one case in Europe, however, it led to a massive manhunt for a criminal labeled "the Phantom" who defied all attempts at psychological profiling. The acts that had been committed were so bizarre that detectives throughout Europe were left scratching their heads. DNA from the same perpetrator, it seemed, had been found at the scene of numerous murderers, mostly in Germany: from three Georgians found in a car trunk in the town of Hesse, to that of a policewoman killed in Heilbronn. But the same trace was discovered on a cookie found in a trailer, a toy pistol used in a robbery in France, and on a rock thrown during a fight between two brothers.

The genetic markers in the DNA from these scenes were clearly those of a woman, and many hinted at Eastern European origins. When the same traces appeared during attempts to identify a body that had been burned in France, however, the police finally realized they had been chasing a fiction – because the body was male. Eventually it was determined that the DNA came from boxes of cotton swabs used in obtaining samples from the scenes. An employee at the factory that made the swabs had accidentally contaminated them, and then they were shipped to various labs.

DNA fingerprinting had applications that went well beyond police work and historical detection. It could also be used to study increases in mutations experienced by people who have been exposed to radiation. Jeffreys



Each line represents a highly variable microsatellite pattern of the person's DNA in the pedigree on the left. The black symbols illustrate those affected by Bilginturan's syndrome. The peaks marked with arrows are common in all of them, but not in the non-affected family members.

has personally carried out an extensive study of children who were born in the aftermath of the Chernobyl nuclear power plant accident in 1986. He found that the larger the dose of radiation that parents were exposed to, the more changes you would find in the microsatellites of their children. That meant you could also expect to find mutations in more important regions of DNA, such as genes.

All of these cases were much simpler than the problem facing Fred's team in Berlin. Matching any two DNA samples involves a "yes/no" question, and the Chernobyl case was a matter of counting. When it came to finding the gene for a disease, variable regions like microsatellites should provide a set of tracks leading to a specific region in one human chromosome. People who inherited the sequence would also inherit nearby microsatellites. Using them, if you found a pattern of inheritance that matched your pedigree, you would know that the disease sequence lay somewhere nearby.

But the genome was littered with tracks, like trying to decipher what had happened on a soccer field after a match in the snow.

Zooming in on the DNA sequence responsible for Bilginturan's syndrome involved comparing every fragment of DNA from a patient with fragments from every other person in the study. When the scientists inspected one of the patient's fragments, they had to ask two questions: "Does every person with the disease have a fragment with the same markers?" If the answer was no, then the cause of the syndrome had to lay elsewhere. If it was yes, the researchers could go to the next question: "Does anyone without the disease have such a fragment?" This time, if the answer was positive, the fragment couldn't be responsible and they moved on to the next segment.

A new system of markers that didn't depend on X-rays, but which could be carried out with just a DNA sequencing machine, was being tested by the company ABI, which Herbert had worked with in Munich and was now supplying equipment for the new lab. The company's probes were dyes that could be detected by fluorescent light. Different probes were designed to attach themselves to microsatellite regions with different numbers of the small, repeated DNA sequences.

A change from Jeffrey's method was the way scientists obtained fragments of DNA from the genome. Instead of chopping chromosomes apart with restriction enzymes, they could now use PCR – the method invented by Kary Mullis – to churn out massive numbers of DNA molecules. They began with DNA that had been extracted from the blood, put it into a PCR machine, and then using microsatellites of various lengths to tell this molecu-

lar "copying machine" which regions of the genome to copy. Each experiment produced DNA molecules of a particular length. "In this case they are indicated as polymorphic DNA markers," Atakan says. "DNA markers can appear not only in one, rather in several respectively defined lengths in the general population."

Now the scientists could run the labeled fragments generated by PCR through a DNA sequencing machine. This could measure their lengths by loading the DNA molecules into a substance called a gel and size determination of the polymorphic markers were carried out with special software. Because DNA is negatively charged, it will migrate towards the positively charged electrode in an electrical field. The gel had honeycomb-like pores that let a molecule slide through, while slowing it down. Its arrival time was strictly determined by the length of the fragment and was recorded when the dye gave off a fluorescent signal.

The DNA fragments were marked at one end with an ABI fluorescence molecule. The system was so precise that you could detect differences between DNA molecules even if they varied by just a single "letter". The same basic procedure, carried out using thousands of machines across the world, would later allow scientists to read the sequence of nucleotides through the entire human genome.

These steps – attaching the dyes, obtaining and copying DNA fragments using PCR, and using a sequencer to measure their lengths – had to be done for the entire DNA sequence of each member of the family. Carrying out the technical work would require months, and Herbert knew he would have to add a skilled technician to his small group to get it done. He advertised the position and began collecting applications.

Since the dye technique was so new that it hadn't yet reached the market, Herbert contacted ABI to arrange to use their probes. When he explained what he wanted to representatives of the company, they were enthusiastic – it sounded like a good way to try out the new system on an interesting scientific project. But it would be best if some of the work could be done at the company's headquarters in San Diego, California, so Herbert began thinking about when he might go.

Preparing the DNA and collecting the data was going to be a tough job, and an equally daunting task now faced Thomas Wienker. The statistical know-how he was absorbing in Jens Reich's group was now going to be essential. He'd have to sort through hundreds of numbers produced from the DNA of each family member, and compare it to numbers obtained from every other family member.

Among the applications Herbert Schuster received as he sought someone to work the new DNA sequencer and other machines, one stood out – that of another young scientist whose parents had immigrated from Turkey. Although Atakan Aydin hadn't originally planned to become a molecular biologist, his interests had led him into areas that were closely related to it, and he had acquired excellent technical skills.

Atakan's father Ismet came from Artvin, a city on the coast of the Black Sea, far to the east of Trabzon on the border to the Russian state of Georgia. He had set out for Germany at the age of 21 after his military service, like the father of Hakan and Okan Toka. "In the Turkish culture, men tend to become philosophers as they reach middle age. My father likes to tell stories, and he has reflected a lot on that important time in his life, and has talked to me quite a bit about it," Atakan says. "Did you know, for example, that all the Turkish immigrants were carefully screened as they entered the country? The authorities even pulled up my father's lip to inspect his teeth! This means that the people who got in tended to be

Hakan and Sylvia

very healthy, and were usually pretty strong. So in contrast to the view that many Germans today have about this large group that arrived in the 1960s and 70s, they were a select bunch. In a way, you might say they were 'genetically screened' before being issued work permits."

Ismet Aydin arrived during the building of the Berlin Wall, first working from 1961 to 1963 in Saarbrücken. The political turmoil had worried so many residents of Berlin – including German laborers – that they left the city in droves at a time when they were needed most. "My father told me that when he arrived, about 80 percent of the roofs had yet to be repaired," Atakan says. This left a gap that had to be filled, so Ismet and many other workers headed for Berlin. He has lived there ever since, returning to his home country occasionally. On one of those trips he met the young woman he would marry. Atakan's mother Baton returned with him to Berlin and worked in a factory while raising Atakan and his younger sister Ayla and brother Cem, all of whom were born in Germany.

Atakan attended the "Realschule," the track in the German school system that usually prepares pupils for technical trades. Atakan is a bit of a technology freak – one of his colleagues laughs about the fact that when a new Apple computer comes out, he can list its features in great detail. (No, Atakan, I won't tell you who, even though it was meant as a compliment.) His teachers pointed out that biotechnology was a booming new field that would offer interesting jobs for decades to come. And there would be equally good opportunities in a related field that had fascinated Atakan in school – ecology.

"The Berlin Wall had just fallen," he says, "and people became aware of enormous ecological problems that had arisen in the East. The former government hadn't shown much concern at all for the environment. In some areas the soil was terribly polluted and the city faced a massive clean-up effort to solve a situation that affected people's health. And there were other problems, such as building new roads and providing energy, which had to be solved with the environment in mind."

After school he found an apprenticeship in a well-known pharmaceutical company that served hospitals and other customers. During the first few months he learned the manufacturing methods needed to make drugs, shampoos, creams, and other products. He learned quickly and had a knack for the technology, so at the end of his training the company offered him a full-time job. He tried it for a few weeks, but quickly realized that he'd never get along with his boss, whose subtly racist attitude Atakan had already encountered too many times. He didn't want it to confront that every day or to be working occasional night shifts when he decided to start a family.

On the other hand, he liked the work itself and had discovered he had the talent to do it really well. But his level of education might one day exclude him from some very interesting projects. The Realschule didn't award the German high school diploma, which universities required for admission. He could still earn it by taking a test, but to pass it he would have to catch up on topics that he'd never had in school. It was possible, of course, for "late bloomers" to change their fate, but it wouldn't be easy. All he could do was buckle down and study.

He passed the test and was accepted into the biotechnology program of the Technical College of Berlin. The program wasn't easy, and he liked it that way; it brought him into contact with intellectual challenges as well as technical ones. It proved he had entered the right field. If you don't like continually facing new puzzles, and aren't highly motivated by finding creative ways to solve them, you don't belong in science. Even the degree and the new responsibilities, however, weren't enough of a challenge for Atakan. A few years later he embarked on a much greater personal task – adding a PhD to his academic accomplishments – although he didn't have to.

In Germany an additional step is required to become a full professor. He tells me he doesn't feel the need. But check in on him in a few years; who knows when he'll decide to climb another hill.

Another thing he liked was the fact that his studies were so interdisciplinary. You never knew whether the next technological jump would come from biology, chemistry, physics, or computer science. DNA sequencing, for example, combined all of these fields. You used chemistry to make a sequencer's gels and to design fluorescent probes that would dock onto particular groups of microsatellites. Physics came into play to detect signals from the probes. And without sophisticated computer programs, you'd never be able to decode those signals.

When Atakan finished his degree, he applied for two jobs – the technician's position that had been advertised by Herbert Schuster at the MDC, and at a company which carried out environmental activities. Both led to an invitation to an interview. Industry offered more money and long-term security. Taking Herbert's position, which was initially limited to a few years, would likely mean that he'd have to search for another job again – but he was highly interested in the Turkish project and other research in the lab. Once he learned his way around new equipment like the DNA sequencer, he would start making a personal and essential contribution toward the discovery of something new.

The situation represented a fork in the road that would probably determine the course of his entire career. He says it cost him a few sleepless nights, and before making a decision he asked the advice of his family and many friends.

Once again Atakan chose the harder path. As Fred would probably say, "In hindsight, you could have predicted it."

Just a few days after Atakan joined the lab, Herbert gave him a crash course in using the new DNA sequencer. The demonstration was so efficient and clear that Atakan realized he had acquired an excellent teacher as well as a new boss. Herbert had praised the magnetic personality and clarity of Fred Luft, who attracted him to Berlin-Buch, and now Herbert was making the same impression on his young lab members.

"He was very encouraging; he'd touch you on the shoulder and say 'Good job,'" Atakan says. "That was quite unusual in Germany. Of course he expected us to work carefully and precisely, but his own technical skills were so good that we had a great example to follow. And he set even higher standards for himself."

Herbert was highly organized and insisted that work in the lab be well-organized and precise. One time Mr. Zhou showed him an X-ray that he'd forgotten to label. "Where's the date?" Herbert said. "Where's the description?" And delivered a short lecture about the reasons for strict lab procedures. He didn't raise his voice, but Mr. Zhou got the point. And so did Atakan, who was standing right there. "You can bet I never brought him an improperly labeled X-ray after that."

Herbert encouraged Atakan and Sylvia to go to seminars and training courses, such as those offered by ABI, and even attend his own classes for physicians. He was still teaching the course on patient examinations that had spawned the relationship with Hakan. Now in Berlin, it was a unique opportunity for two young molecular biologists and they jumped at the chance.

"I don't think many groups would have gone to the effort to fly off to Turkey," Atakan says. "But fieldwork is crucial to genetics; we might need to do it ourselves one day. And then you'd need to know certain basic things in dealing with patients, like how to draw pedigrees, which Herbert covered in the course."

Knowledge and experience had to flow in two directions, and Herbert was just as determined that the physicians in his course learn about what went on in the lab. Atakan was surprised at how little they knew. He had only witnessed the culture gap from the perspective of molecular biology. Why didn't doctors want to know more about the illnesses they encountered every day? And who would they learn it from, without extra efforts from physicians like Herbert and Fred?

Atakan had never really considered "molecular medicine" from the clinical point of view. They approached diseases so differently, asked different questions, sought different answers, and even had daily schedules that seemed almost incompatible. The biologists believed that finding cures for hypertension, cancer, and other diseases would require a deep understanding of their underlying causes. It was hard to tell how long that would take, and turning knowledge into a cure would surely take much longer. But physicians had to cope with the patients sitting in their waiting rooms, who couldn't wait that long.

Bridging the gap between these cultures would take dramatic, creative efforts to establish common ground. The kind of teaching that Herbert was doing seemed to be a good place to start, and Fred felt the same way – he'd been pushing for new types of training throughout his career. But such people were rare; in most cases you'd have to go a long way to find another. Having two on the same campus seemed like incredible luck, but it gave Fred and Herbert a chance to implement some of their ideas about training. In doing so, they were fulfilling what Detlev Ganten had hoped when he hired them.

Pinpointing the location of the damaged DNA would require at least several months of effort, even with the whole team working according to a very efficient plan. In the meantime, there were two things that had to be done very quickly. Thomas, Hakan, and Fred had to make a trip to Stuttgart. Okan had already returned to Munich to continue his studies, so he couldn't come along. He'd be back soon, to help with the visit of several of the family members to Germany. They were coming for the extensive studies that Fred wanted to carry out in the clinic in Berlin. He had talked this over with Cafer and Ali, and they would come as soon as the details had been worked out on both ends.

Within two weeks of their return, the scientists got in touch with the family in Stuttgart, who sounded interested and were willing to meet. The trip give Fred and Thomas their first opportunity to communicate directly with affected family members without the need of an interpreter, which was a relief. Hakan still did some translating when their German faltered, but at least you could make yourself understood.

At the family's house, they were greeted with the same warm hospitality that had marked their arrival in Turkey. The mother was a member of the "new" branch of the family whose discovery had spurred the trip up to the Yayla, and she was affected by the syndrome. Her brother, who was unaffected, had been the first to arrive in Germany; he had arrived alone in 1978, and was joined by his sister and their parents a little later. Some of their older siblings had remained in the Black Sea area.

The young woman had met her husband, another Turkish immigrant, in Germany. He worked in a company that produces car parts and today wears his hair in a big black swath that reminds Sylvia of Elvis Presley. The brother and his children were there, as well as the woman's two daughters, who were unaffected. One of the girls had just started school, Hakan says; the other was still an infant. A few years later two boys came along: The youngest is also unaffected. But his older brother Bülent, whom the group met in 2012, has turned out to be unique in the

family. The syndrome has affected him in a slightly different way than all the others, which might turn out to be very significant.

All of the relatives in Stuttgart agreed to take part in the study and permitted samples to be taken from the children. Fred and Hakan asked general questions about their medical history, got out the blood pressure cuffs, and pursued any issues that arose. An important fact quickly emerged: the woman's doctor had noticed her high blood pressure, likely during her first pregnancy. But he didn't ask for a family history, and remained unaware of the unique genetic aspect of her problem.

As a result, the physician had treated her like anyone else who arrived at his door with essential hypertension, prescribing drugs and watching her response. He probably had to try a few times until they found a combination that worked; she was now taking two or three different drugs.

When Fred took her blood pressure, he found values of 130/90 – well within the normal range for a woman her age. "If you think about it, this was pretty remarkable," he says. "Without noticing anything 'different' about his patient, her family practitioner had done just the right thing. It was another good sign that we were dealing with a form of essential hypertension. And it made it a lot more likely that other people in her family might be treatable with existing drugs."

Which meant that the sooner they could get a drug trial going, the better.

As the trio from Berlin made their way home from Stuttgart, Cafer and four of his relatives were getting organized for their trip to Berlin. Cafer was the only one who'd ever been out of the country, or even on an airplane, when he had accompanied groups on pilgrimages to Mecca. None of the others had passports. Getting them would require a trip to Ankara, where they had to apply in person.

So now the group faced two journeys. The first, to the capital, was already an adventure; the second, to Germany, lay so far outside their experience that the whole idea seemed unreal.

12 A family in the world

They arrived in Berlin in December, 1994: five small people following in the wake of Cafer, who was easy to see because he was a head taller and conveyed the impression that he knew what he was doing. In the future, he would fly many times as he led groups on the pilgrimage to Mecca – a lifetime ambition for Muslims. This trip could be considered a sort of practice, and he considered it his duty to make them all feel safe. Each had volunteered, but only because he and Ali had agreed that the trip was a worthy thing to do. Then Cafer had presented the idea to their relatives, so he felt responsible for everything that happened.

He never made such decisions lightly. As this book was written, we had to consult him several times. Even when a request seemed small, he weighed it carefully, considering all the potential implications for his family and community and putting their needs first. He is a natural leader and a modern one: He is well aware of the way the world is changing and knows that his people must not be left behind. At the same time he is determined to preserve the things they cherish. Keeping the balance requires decisions great and small, and sometimes it's hard to tell the difference.

When I met him many years later, I asked why he had so strongly supported this scientific project over so many years. A lot has been asked of his family, and at every turn they

have come forward with a remarkable willingness to submit themselves to uncomfortable tests. His answer came immediately, and it was quite simple: "For the human race, for my family, and for my faith."

This simple answer encompassed so many things. Fred had told him that studies of the family's health might help scientists understand a very serious problem that affected nearly a quarter of the world's population, and Cafer took that statement very seriously. A little discomfort could be tolerated if there was a chance to do so much good, even if Fred couldn't guarantee results.

On the other hand, Fred was also a physician. A lot of drugs had been developed to treat hypertension over the past few years, he said, and one of them might lower their blood pressure. Finding the right one, or a combination, would take time and before you started, you needed the clearest possible diagnosis. That would narrow down the number of drugs you'd need to try. And Fred *would* try. Cafer sensed that Fred didn't give his word lightly, either.

"So this project could help other people?" Cafer had asked.

"It could help an awful lot of people," Fred said. "Eventually."

"And the drug study could help my family?"

"If we can find something that addresses the symptoms, something that lowers their blood pressure, I think we can add years onto the lives of the people right here. Maybe a lot of years."

In the short term, the family needed a physician; in the long term, the world needed the science. Cafer had a deep appreciation that sometimes, the fate of the individual and the world were linked. He confronted this fact every day in the opposite sense: technology and change were rolling into the villagers' lives. Rarely did things work the other way around.

Here was one of those exceptional cases. For someone like Fred, the link was personal: Meeting affected people directly awakened all of his instincts as a physician; these were patients, rather than abstract subjects of a research project. You couldn't help it.

It made Cafer's decision fairly simple. No one in his family had ever regarded their condition as a curse, or something to be ashamed of, but nobody had ever considered it a blessing, either. Suddenly, just by looking at it a certain way, that is what it had become.

And it also put a certain responsibility on the family. The genetic accident that produced Bilginturan's syndrome might have happened to anyone, but it hadn't. It was here, in this family, and because of that, Cafer helped turn it into a source of hope.

So the family flew to Berlin. I have imagined this scene many times. Years later, when we flew back from Turkey, I tried to see our trip through the eyes of Cafer's family. It was impossible, of course, to trip some mental switch and make what had been so strange in Turkey into the familiar, and to observe all the trappings of air flight as if I hadn't flown a hundred times. But I imagine it something like this:

As Cafer led the way through the airport, Ali's eyes roamed behind the thick lenses of his glasses, inspecting everything. Mehmet seemed as unperturbed as always, and the three women, Benan, Adile, and Kezban, discussed everything they saw. You had to stay constantly alert. It was crowded, and people were rushing around far too fast, and a cart might swerve into your path at any second. It was hard to tell what line you were supposed to get in with distractions clamoring for your attention from every direction.

They placed their bags on the conveyor belts and watched them disappear through a hole into the mysterious depths of the airport. Cafer had warned them about the security check, and they submitted meekly, but it wasn't pleasant. Then there were the seats in the plane that might lean backward at any moment without warning. The safety demonstration hinted at strange perils involving life vests and air masks. They paid close attention; never having flown before, it was hard to tell how often these things happened.

Kezban had found one of the air sickness bags and was about to ask Cafer about it when the engines started up, their stomachs lurched, and a sudden acceleration pushed them deep into their chairs. The plane was a lot bigger than the last one and it seemed to roll a lot faster. Would you feel this way the whole flight?

Kezban suddenly figured out what the bag was for.

They kept their noses pressed to the windows. There had been fog in Trabzon but the midday sun had swept it away, and now had their first view of the world from the air. Amazing. The sky was clear over Switzerland and the high mountains were plain to see; they looked like a map, but seemed etched in infinite detail. Tea was served – not very good, and it left a strange taste in Ali's mouth – followed by lunch. A stewardess showed them how to lower the trays on the seats in front of them. It was hard to eat on the little tables; you had to keep all your food jammed up together.

As they chased the sun over the long afternoon, the plane flew into a cloud. Everything turned grey outside. "I'd rather be driving," Mehmet said. But he said that when he walked somewhere, too.

Adile thought they ought to do something with their dinner trays but was too scared to get up. That took care of itself, and the plane began its long fall toward Berlin. Another strange feeling in your stomach. Then a very hard bump as the wheels hit the ground, and it seemed to be trying to stop too fast.

Hakan Toka had arranged an inexpensive flight with a transfer in Switzerland and found someone to help guide the family through the airport. They went through the strange process of passport checks; Cafer produced an official-looking letter from Fred Luft that got them right through. The luggage carousel was interesting, and it brought the bags up from a hole just like the one in Trabzon, almost as if the luggage had raced along through underground tunnels as their owners zoomed through the air. Then they faced the universal human challenge: They knew what their bags looked like, approximately, but now you had to spot them among hundreds of other suitcases. What would happen if you took the wrong one? Better to let them go around a few extra times and be sure.

In Berlin they followed the crowd and were infinitely relieved to see two faces they knew outside. Hakan and Okan were standing right there. They greeted each other. "How was the flight?" Hakan asked, and everyone started talking at once. They had a lot to say about that.

It was dark outside. They climbed into a huge rental van and, as exhausted as they were, peered out at the amazing arrays of lights that marched off to the horizon in every direction.

The rooms were spacious but as subtly strange to them as their houses in Karamat had seemed to us. In Cafer's house and the other places we visited, I noticed that every carpet, every scarf, every carpet and drape was ornamented with flowers of vivid colors. Here everything was monotone, and that must have seemed drab.

Fred and Herbert arrived and the Tokas made tea. As they sipped they talked about the flight, then the brothers spoke briefly about the program for the next morning, trying to keep it light. Cafer had been given the details on the phone and had passed them along. So they all knew

Okan

what they were getting into, but it was still bound to be a shock. Hakan hoped to ease them into it, but from the way they talked, it wouldn't be any stranger than their first ride in an airplane.

There were forms to be filled out. If they were too tired to do it now, they'd have time in the morning. Hakan gave Cafer a pager and showed him how to use it. During the days in the hospital, he promised, at least one of them would be in their room all the time. At night they would sleep here in the guest house, but it was right next door to the clinic, and the brothers would be permanently on call. If someone needed anything, for any reason, they should use the pager.

Hakan looked at his brother. "Did we forget anything?"

"I can't think of anything," Okan said. Fred couldn't either, and nor could Herbert. The brothers would be back for breakfast. Tonight they would be just down the hall.

"Let the fun begin," Fred said.

They didn't try to translate that.

Before a doctor prescribes a drug he needs a diagnosis, and the family's high blood pressure initially looked like essential hypertension, but the group hadn't been able to carry out some of the most desirable tests in Turkey. The family's genetic defect might be a vital clue to the reasons other people developed hypertension, but only if you were sure that's what you were dealing with.

Hakan and Okan had planned a broad range of tests to answer the question and also to take a closer look at the family's overall health. Hakan was worried about what they might find. If hypertension goes untreated for too long, it usually causes kidney damage, an enlarged heart, a thickening of the arteries, or other problems. If you got the blood pressure under control quickly enough, the problems might not be too serious; otherwise they might have to be treated in their own right.

Sometimes things happened the other way around – a narrowing of arteries in the kidney, for example, could set off a chain of events that led to hypertension. Blood pressure may also rise if the body produces excessive amounts of certain hormones. In these cases and several others, scientists have a pretty good idea of the connection between the cause and the effect.

It starts with the fact that our bodies contain a huge amount of water. Drinking and eating add to the overall supply; they bring fresh water into the system, and then it gets recycled many times. The kidneys act as a filtering and recycling plant that reabsorbs water from the blood and uses some to flush out wastes in the form of urine. In general, they ensure that the overall amount of water stays the same. Sometimes this requires absorbing more, especially if you're losing a lot of it water and have a hard time replacing it – when you're riding in the Tour de France, or wandering around in the desert. But the level of recycling also rises and falls over the course of a normal day, because our bodies shed water all the time. And this has a direct effect on blood pressure: it falls if water is removed from the bloodstream, and rises if water accumulates.

The kidney often can't decide what adjustment is necessary entirely on its own. It relies on a sophisticated system of sensors spread throughout the body that often communicate via hormones. Some of the sensors are directly attached to arteries, where they act like mini blood-pressure measuring devices; others monitor the system in less direct ways. They may communicate directly with the kidney, or route information through the brain. There, signals can be sent through the autonomic ("involuntary") nervous system, telling muscles to squeeze the blood vessels that supply the kidneys and reduce the flow of blood passing through. Certain types of hormones achieve the

same thing by docking directly onto the muscles and causing them to contract. Both actions reduce blood flow to the kidneys and change the rate of water reabsorption.

Hormones create the feeling of thirst as well, but it takes time for new water to enter the system. Your kidneys usually get thirsty before you do.

It's a complicated system, so there are lots of places where things can break down. That can happen for mechanical reasons – such as damage to the kidney or the muscles around arteries. It can also happen if a signal never gets sent, or isn't interpreted properly. Any of these situations can lead to hypertension, by preventing the kidney from interpreting a signal, getting it in the first place, or responding in the right way.

But in each of these cases, abnormal blood pressure can be traced to a specific physical problem. Or a genetic one: for example, a mutation may prevent the body from producing one of the hormones needed to regulate the system. And then the problem is called *secondary hypertension* (because it happens second, after something else.

Essential hypertension isn't that way. Researchers don't know where it begins – not in any of the places you'd think to look. Even in the absence of some clear cause, the whole system breaks down. It was beginning to look like one of those fuzzy cases where the ultimate problem might lie in a combination of variants of several genes, whose behavior goes on to be influenced by complex environmental effects. Such cases were almost impossible to decipher.

Here the problem was monogenic, and suppose you could eliminate all the usual suspects in secondary hypertension, including mechanical problems and other genetic defects known to interfere with things like kidney function. Then you'd slide into new territory, because you'd have your hands on a case of this "nonspecific" high blood pressure that stemmed from a single defective bit of DNA. It had to influence *something* in the body – and they already knew that it did: the building plan of the skeleton, and of fingers.

It also had to be doing something else. No one seriously thought that people had high blood pressure simply because their fingers were too short. Whatever was going wrong lay with a part of the vasculature, the nervous system, or a biological process that no one had yet connected to the condition. That was exciting because there was a chance, Hakan and Okan thought, that the work in the hospital might reveal that one unique thing in the family's bodies.

And if they found it, they could go back to all of those millions and millions of cases of hypertension that remained unclassified. Maybe they would find it there as well.

Even if you were engaged in a great project to help mankind, after three days in the hospital, nerves could wear thin. And there was still half-way to go. The six family members lay on their beds in the Franz Volhard Clinic and talked to each other, or thought about home, or simply counted the minutes. Until a nurse came by again to draw blood, or do something to the bag from which an infusion oozed into the needle taped into your arm, or have you drink something that made you go to the bathroom all the time.

Drip, drip, drip.

Cafer occupied one of the beds, submitting to all the same tests. He didn't have the syndrome, but he wasn't about to put his family through something unless he was willing to do it, too. And he was an important control: pieces of his DNA were scattered throughout the bodies of the others.

At night the blood pressure cuff puffed up at regular intervals, the first few nights waking you up every time,

Ali, Thomas, Hakan, a clinician, Okan, Herbert, and Mehmet

Cafer, Thomas, Ali, Herbert

Atakan

leaving you groggy all the next day; the second night you noticed it and tried to fall asleep before it started again; the third day you felt surreal.

Cafer devoted his energy to staying calm, asking Hakan how the women were doing in the other room whenever he came by, and counting the minutes.

Ali looked out the window, thinking of his hazelnut trees and wondering what his wife was doing. He was 46 years old, well into the danger zone of mortality for the men in his family. He wished he could get out of bed more often to pray.

Hakan and Okan drew blood, carried samples to the lab, and talked to the technicians. Every day had a strict schedule. They checked levels of hormone after hormone in blood and urine, crossing them off the list of possible causes. They measured blood pressure before and after the saline infusions, which increased the amount of fluid flowing through the patients' blood vessels. This changed not only their blood pressure, but the hormones running through their bodies. Their systems were trying to tell their kidneys to stop taking up fluids, not knowing that the kidneys weren't responsible.

After the patients went to the bathroom in the morning, they mounted a scale to be weighed. Then it was back to bed, unless you needed to be carted off for X-rays or some new test. There was no telling what form of torture the scientists would dream up next. But boredom was worse.

Hakan and Okan regularly checked the tape of blood pressure values, wrote things down on charts, and after a few days did some statistics. They noted that there was a strong correlation between the level of the blood pressure and a patient's age. Older meant higher.

Ali held the record for a blood pressure measurement, at 250/150. One day Okan appeared with a doctor he didn't know, who looked at Ali's chart and made a low whistle at what he saw.

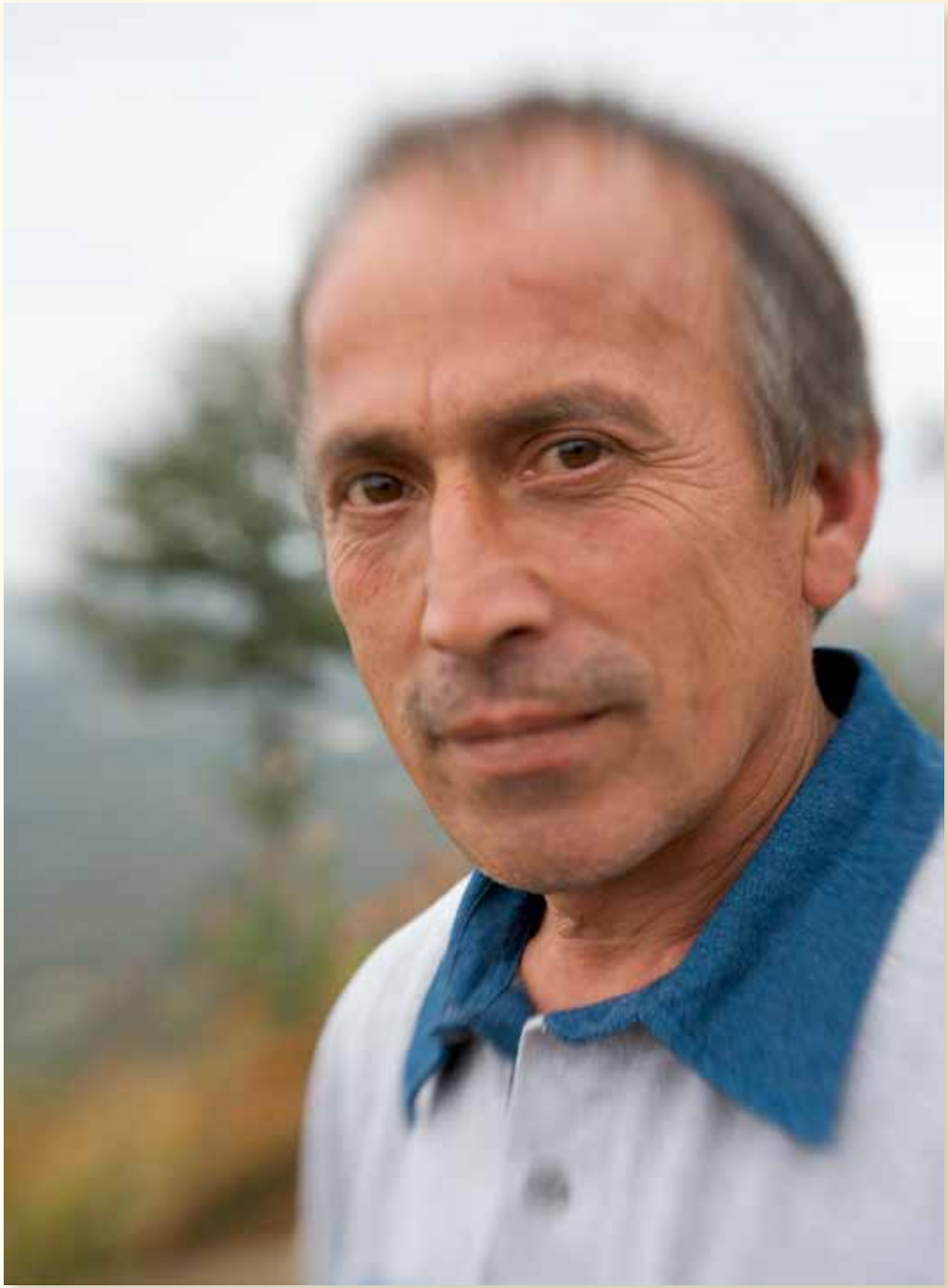
None of the patients exhibited any narrowing of the kidney arteries, another thing to check off the list. Their thyroid and adrenal glands were working fine. They produced normal amounts of urine, with no signs of abnormal proteins. Maybe the biopsies would show something.

Fred Luft came by from time to time and gave them a sympathetic smile that seemed to say, "I know, I know. Sorry about all this." On the first morning, when they had checked into the hospital, just as they were about to walk in the front door of the clinic, he had ridden up on his old bicycle. No one recognized him until he took off his helmet. They could see his white coat hanging down under his winter jacket, and a small tear in his pants. They all stared in amazement.

"A doctor in Turkey," Okan told him later, "never goes anywhere without a little procession of helpers. A driver, maybe a younger doctor, an assistant whose sole job is to make tea whenever he presses a button in his office. You would never catch a Turkish doctor dead on a bicycle."

Cafer was terribly impressed by this. It was more evidence that Fred Luft was an honorable man, someone who didn't need to put on airs to establish authority. All of his young colleagues seemed at ease with the professor. He recognized that Fred, too, was a leader, but one who had no need of arrogance to earn the respect of his colleagues.

The young doctors eliminated known causes of secondary hypertension one by one. They took a urine sample from each patient every day and checked it for more hormones, electrolytes, concentrations of calcium, phosphate and magnesium. All of these substances were involved, in one way or another, in the regulation of hypertension. Once again the tests that were performed ruled out known forms of secondary hypertension.



Mehmet

Two of the women volunteered for examinations in the MRI machine, mostly out of boredom. They lay on a table, which slid into a sort of tube where they had to lie as still as possible for about half an hour. The whole time Kezban needed to scratch her nose, which was driving her crazy. They had tiny, foam earplugs stuffed in their ears, but the clacking sounds made by the machine were startlingly loud.

A doctor named Christoph Tahlhammer came by and peered into their chests by ultrasound. Mehmet wanted to know how the machine worked.

All of them watched the monitor to see what was going on in their chests. Christoph took measurements; he wanted to check the thickness of their arteries. He found that the walls had thickened, which you would expect – you'd hope so, with a pressure nearly double the normal values.

There wasn't anything good on TV, at least not in Turkish. A doctor named Albrecht Hempel came by, picked them up, and took them to a room with another machine and a table. Another wand-like instrument was pressed to their chests. Albrecht wanted a look at their hearts.

"That's my heart?" Ali asked. He saw a grey thing pulsing and squirming around, like a fish in a net.

Mehmet asked how the machine worked.

The images obtained through the procedure revealed that the affected people had hearts that were mildly enlarged. Not enough to be particularly alarmed about, which was amazing, giving the amount of force that the organ had to produce to push blood at such pressure through the arteries. Once again, this hinted that along with the other characteristics, something about the family protected them from most serious side-effects that accompanied most forms of hypertension.

Everything they were discovering about the syndrome confirmed that it was unique among all the other known monogenic forms of hypertension. All of them had turned out to fit the secondary hypertension category. One more important test supported this.

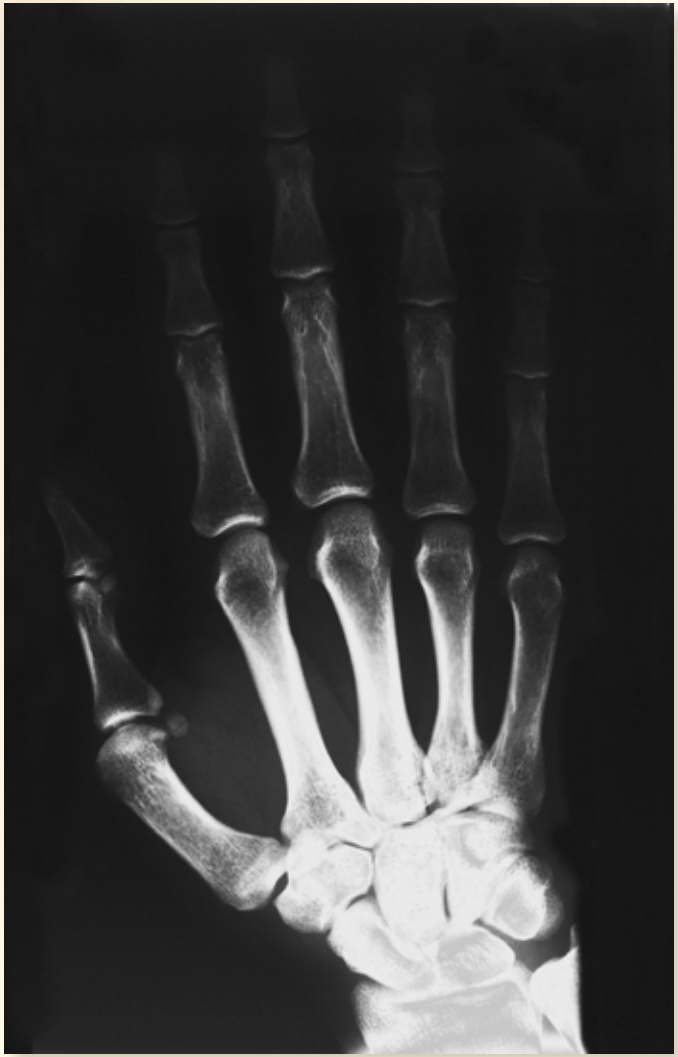
The solution that the family had been receiving by infusion, which added fluid to the circulatory system, contained salt. "Just about every form of secondary hypertension we know of," Fred says, "is accompanied by a sensitivity to salt. When a person with secondary hypertension – and to some extent a healthy person – eats it, you usually see a jump in blood pressure that lasts for hours."

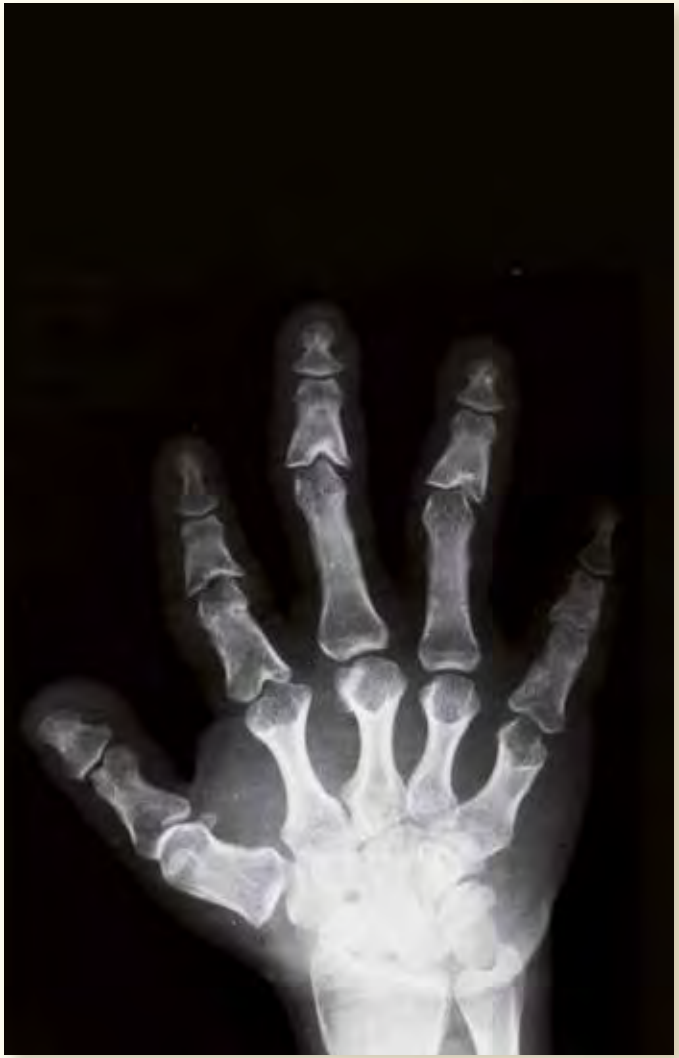
The reason has to do with the cells that line arteries, which are sealed together by tight bonds that prevent leakage. But charged particles called ions can pass through cell membranes and the lining. Once in the bloodstream, salt is broken down into its basic components: sodium and chloride, and both are ions. The kidney can shuttle them out of the body, but in the meantime, pressure builds up inside the vessels because they are retaining water.

This doesn't happen in essential hypertension, however, and increases in salt didn't cause a significant rise in blood pressure in the five people with Bilginturan's syndrome. Another bit of evidence.

They went to have their hands photographed and X-rayed. Later Hakan looked over the images with Sylvia on the light machine. Adile and Benan had been let out of bed and were walking around; Hakan put up the images from Cafer next to the X-rays of the two women's hands. One non-affected and two affected. The scientists looked for a while and then began discussing the bones of the hands. Hakan translated while they talked.

Sylvia used a pen to point out regions and features of the bones. Human fingers came in so many varieties that you had to get used to "normal" ones before tackling the





problem of all the short-fingered types. In this case, the difference was so extreme that it stood out dramatically.

"These are the metacarpals," she pointed, tapping her pen over the bones that ran up from the wrist to meet the knuckles. "The fingers start here. These bones are called phalanges." She held her own hand up to the light box, to compare the skeletal image to a hand whose flesh hadn't been stripped off through the magic of X-rays.

"Can you see a difference?" Hakan asked the women.

The two women squinted and discussed it for a minute. They noticed that their own metacarpals were much shorter than those of Cafer. The fingers themselves looked pretty much the same – a bit shorter, but with about the same proportions. They delivered their verdict.

Sylvia pointed out another difference: the two metacarpals on each hand adjacent to the thumb were a bit longer than the last two, which were little more than stubs. So while the phalanges of the little finger and its neighbor were of normal length, they seemed much shorter because they started closer to the wrist. The tips of the bones ended in rounded shapes – *epiphyses* – rather than the flatter connections found in the hands of healthy relatives.

As the women walked back to their room, they couldn't stop looking at their hands, which were so special, they had their own name. Their hands would never look quite the same again.

"Metacarpal," Benan said.

"Metacarpal," Adile repeated, and laughed.

Still nothing good on TV. But the women kept it turned on sometimes and had long discussions about what was going on. They made up ridiculous bits of dialogue for the characters, and outrageous stories about their relationships, which made them laugh so hard that Kezban had to go to the bathroom.

Benan kept looking at the hands of the women in the film. "Metacarpal," she said, and Adile laughed again.

After being puffed up with fluids, the patients were given diuretics, which made you urinate a lot. All the time, the blood pressure cuff expanding, then leaking out its air. The blinking automatic machines that did the work had been interesting for a while, but anything got old after you watched it a thousand times.

Evi Jeschke came by the day they received a local anesthetic. She waited in the corner, talking to Hakan with a smile on her face, as one of the doctors cut a slice from their arms and applied a bandage. The little slice of skin was placed in a round dish that Evi took away. The idea was to extract cells called *fibroblasts* – oddly shaped cells that grew in the skin and connective tissue and helped in wound repair. Evi collected them and took them to the lab.

"I think she has a thing for Hakan," Mehmet said.

"Who?" Ali said.

"That woman."

"What woman?" Ali had fallen asleep and now fumbled for his glasses on the little table by the bed.

Evi discovered that the fibroblasts of the affected family members grew faster than those of Cafer, and faster than the norm for healthy people from other families. That was interesting because a similar phenomenon had been found in laboratory rats that had hypertension.

The next time Evi came in, Ali's eyes followed her around the room, magnified to the size of big black marbles by the thick lenses. She would have said something, but the man wouldn't have understood.

"Why does stare at me all the time?" Evi asked Okan, who shrugged.

Ali

Cafer couldn't understand them, but with his fine antennae for human nature, he knew that something was going on. He winced as Okan stuck a needle in his arm.

"What did she say?" he asked. Okan shrugged.

"She has a thing for Hakan," Mehmet said, and Okan laughed.

"I can tell you a story about that," he said.

Downstairs in the lab, Sylvia, Thomas, and Herbert were meeting with a representative from ABI to talk about the search for the gene. The representative was talking about the new markers that the company was producing. "They are still under development," he said. "They're a beta version." He talked about the differences between the DNA sequences that the dyes would bind to, and their intervals along the genome.

The benefits of the partnership that was being established were mutual. Herbert and his team would need access to the new markers, and the company would be able to test its system in the context of a real scientific project. It would give them the chance to discover any bugs that remained, and the group in Berlin would have excellent support along the way.

The company extended an invitation to Herbert to carry out part of the project at their headquarters in Foster City, California, near San Francisco. He had discussed it with Fred. It might not be the best time to leave – the group had only been working together for a few months – and would probably slow down some of the other projects he was pursuing. But he was confident that Sylvia could manage the lab, with Evi's help – there would certainly be enough to do as they searched for the gene – and she would have the support of the new technician that he had just interviewed – Atakan Aydin.

They quickly mapped out a plan for the work. Herbert in California and Sylvia in Berlin would have the same system at their disposal, including any updates or improvements that would be generated along the way. There were 22 pairs of chromosomes to examine – since children of both sexes could inherit the syndrome from a parent of either gender, it meant that the trait wasn't linked to the sex chromosomes, the 23rd pair. Sylvia would start at one end of the genome and Herbert would start at the other, comparing their findings, eventually meeting in the middle. With a bit of luck, the trait might be found on one of the first chromosomes they examined.

Thomas would sit at the center of it all, receiving e-mails from both of them, containing numerical values for each bit of DNA that they examined into a numerical value. The numbers would be plugged into a statistical program that would have to be heavily adapted to the situation. Its job would be to run comparison after comparison: each fragment of each affected person against the same fragment in every other affected person. If that particular segment were the same length in all of the subjects, it would then be compared to the results in healthy family members.

Thomas had few illusions about the complexity of the task, or the time it might take. "We were taking on a mapping project that covered the whole genome with an extremely large family," he says. "Even today, this is a very difficult methodological undertaking. To do a linkage analysis, you have to make likelihood calculations. You would have to build a formula that – if you wrote it out in normal handwriting – would extend about four or five meters."

He says that even the best computers today can't handle such a problem beyond a certain size. "And in those days, the computers weren't that powerful. The basic programs were there, and I had worked with them. But they would require significant adaptations."

450 segments of DNA – the number of regions between the microsatellites marked by dyes – would have to be compared in over 40 family members. "The real issue was to break it down into smaller routines that could work on subsets of the information, and then link them together," Thomas says. "There was no single way to do this, and if you make a mistake, you get false signals."

Or you might miss something. Both the work with the DNA and the computing would have to be flawless. "When I realized that the pedigree was so complex," Thomas says, "I had this fantasy of buying a plane ticket to the Caribbean and never returning. In the end I decided to stick around for a while."

Outside the air was freezing cold, but freedom had never been as sweet to the patients. The work for the scientists was just beginning – the study in the clinic would form the topic of Hakan's PhD dissertation. But the week had been exhausting for them all, and Hakan and Okan were ready for a break. They would get it playing tour guides for six very patient visitors from Karamat, who were ready to break out and have an adventure. The visitors had two days left to explore a vast city so far from home that it seemed like the other end of the world.

The Toka brothers made a plan that would cover some of the most impressive parts of Berlin, such as the Alexanderplatz, with its huge television tower looming over the city. If the group wanted, they could take an elevator to the top and catch a view of one of the world's largest cities, sprawling across the vast plain. At the moment it wasn't very attractive. The skyline was covered in so many construction cranes that you couldn't count them all. A period of frenetic building had begun after the fall of the Wall, an urban rush led by speculators who had moved in, bought vast tracts of city blocks from their owners in the former East – for what seemed like fortunes at the time – and hoped that prices in the city would skyrocket.

One stop on the tour was a visit to relatives of the Tokas in Berlin, whose home offered an interesting mix of the familiar and the new. And of course there was shopping, which couldn't be neglected. Many of the family members had been to Ankara, the Turkish capital, and a few had been to Istanbul, almost equally impressive and strange. But Berlin had the Kurfürstendamm, the Champs-Elysée of Berlin, where large, expensive boutiques with high windows lined a wide pedestrian street, full of tourists of all nationalities, as exotic to Cafer and his family as the bazaars of Ankara and the coastal towns had been to us.

"We walked down the Kurfürstendamm," Hakan says, "and everybody – I mean everybody – stopped to stare. I didn't get it at first, because there was nothing really strange about their clothing, or their behavior. Then I realized that Okan and Cafer and I were walking along ahead, and the other five behind us, and they were *short*. All five of them were short. It didn't stand out as much in Turkey, where I guess the average height isn't that tall, but in Germany the people are a lot taller. Needless to say, we stood out."

For Hakan and Okan it was a chance to see a city and culture into which they were perfectly integrated through the eyes of Ali, or Benan. One of their stops was the *Kaufhaus des Westens* – still advertised as the largest department store in Europe – and things got bogged down right inside the door. "I didn't realize they had never been on an escalator before," Hakan says. "They stood at the bottom and watched it for a long time, highly skeptical. When we finally got on, they held onto the rails for their lives."

The store seemed to have everything in the world; it went on forever.

One stop was the gourmet selection, with wide counters and a panoply of international delicacies. Okan bought some slices of baguette, adorned with pink stripes

of salmon. They sniffed at it, peeled off the salmon and put it to one side, and ate the bread.

"This is wonderful bread," someone said.

"Of course they would never eat raw fish," Hakan says. "It was something we should have thought of. But they *really* liked the bread."

The most amusing moment of the day, though, he says, had happened a little while earlier. And it had come at his own expense. For the weekend he had rented a big van that they could all fit in, and maneuvered it along the Friedrichstrasse in the city center until he saw the sign for the parking garage under the department store. He drove down the ramp, collected the ticket, and started to drive inside. Then they all heard a scraping sound, and looked up.

"It hadn't occurred to me that the van might be too tall," he says. "The ceiling was too low; I'd never get it inside without ripping off the roof."

And turning around was completely impossible. The only solution was to back all the way up the ramp.

"It was Saturday morning, and the ramp was already full of cars," he says. "Behind those were other cars backed up behind them, all the way up onto the street." He doesn't remember how long it took for all of them to back up – "A *long* time," he says, "and I probably left Berlin in a gridlock for hours.

It didn't help that they were all laughing so hard; well, at least he'd given them a story to take home and repeat for years. On the way to the airport, as they boarded the plane, someone needed only say "Van," and it would break them up, over and over. He imagined them laughing all the way home.

Once there, they would have new material for weeks and weeks of conversations. And every time they told the story of their trip to Germany, they would end with the story of the van.

13 Linkage

Sylvia Bähring still has the notebooks full of data, and the big chart is still pinned to the wall of her office. The books contain hundreds of pages of graphs collected over endless months of routine. Day after day you waited for a signal. As she describes the way she spent 1995, I think of those hopeful radio astronomers who listen to the static of space for an extraterrestrial signal that might never come.

In this case, there *had* to be a signal, but there was no telling whether it would arrive in March or December. In Berlin, Sylvia and Atakan and the lab had been working toward the center of the human genome from one end, while Herbert Schuster and a group in Foster City approached from the other. Now Sylvia and Herbert were about to meet in the middle. Bilginturan's syndrome had few places left to hide.

The chart of the genome on her wall was marked with the positions of the microsatellite tags, labeled with numbers called *LOD scores* obtained from Thomas Wienker's analysis. If a score rose to three, she fully expected confetti to fall from the ceiling, a band to start playing somewhere. But the values hovered just above zero.

Every number you filled in was one less you would have to write.

Atakan came in for a cup of coffee, which meant that the PCR machine was running, or the sequencer, or mabye both. Every day his first act was to retrieve a tray with DNA samples representing 36 patients. He used his pipette to transfer a miniscule amount into tiny tubes, which went into the PCR machine. Later he would take the tubes out, now containing billions of copies of one fragment of DNA, representing the same fragment of the same human chromosome from each patient. He carried out a quick test to make sure the machine had done its job, then loaded the samples into the sequencer so that they could begin their slow crawl down the gel. The laser at the bottom detected the fluorescent dyes attached to the end of each fragment, revealing its size.

He was excited about his job, but the steps were tedious and he had to pay careful attention. Today most of these steps can be handled by a robot, and knowing Atakan, he can probably run it all from an app on his iPhone. But at the time, the lab's only robot was Atakan.

The coffee machine was on the table by the door, but his cup was on the desk in the back. Sylvia handed it to him so he wouldn't have to climb over her. He looked into it and frowned, then went back to the lab to wash it out.

Sylvia recorded the lengths of the fragments, converted them into tables, and sent them by e-mail to Thomas, over at the MDC. He plugged them into his statistical formula and hoped that the numbers would form a pattern that matched the pedigree: the length of the fragment in all the affected people should be the same, yet different from the value for everyone non-affected.

Atakan had time to get a coffee while the sequencer carried out the run. When it finished, he got the machines ready for the next run, and started all over again. He'd do that all day, then he'd go home, then come back in the morning, and repeat the process with the next regions of the chromosome. Day after day, month after month.

In the time it took him to wash his cup, Hakan had come in. They barely saw him these days; he spent his time at the medical school or some clinic, doing whatever it was that medical students did, except for the few hours a week he would come over to work on his dissertation. He was still writing up the results from the family's visit a few months ago. When he came in he started spreading out paperwork in front of the computer.

"You guys look exhausted," he said. "You ought to go to a conference or something."

He had made the same pronouncement couple of weeks ago, and out of the purest form of boredom, they'd spent an hour trying to come up with the most outrageous topic for a conference they could think of. When Herbert called later that afternoon, Hakan had been nearest the phone. Pretending to be serious, he asked if they could all go to a conference next week, in Nice, France, on protein crystallography.

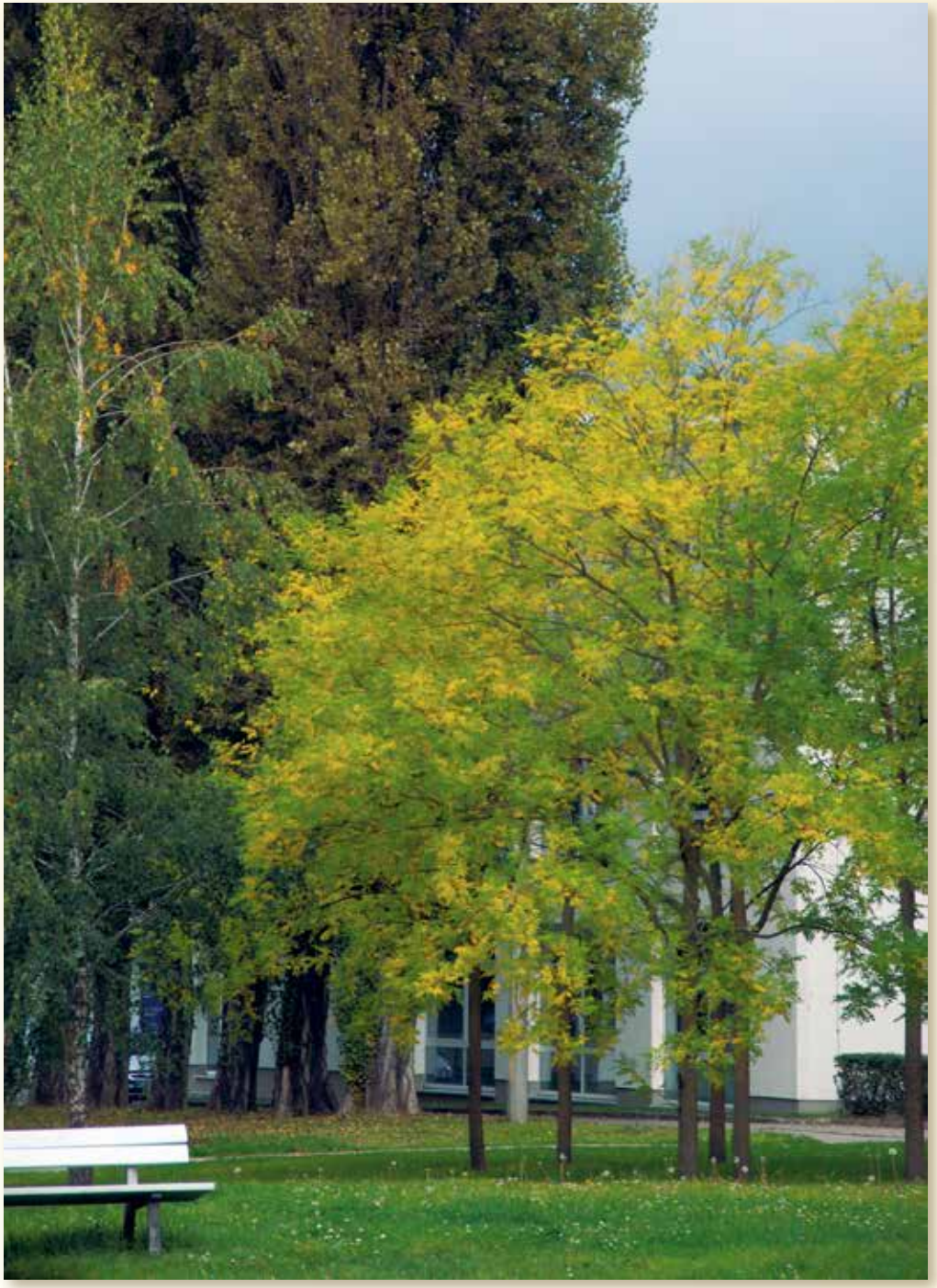
Crystallography was not something any of them could possibly have been interested in, but even so there was a momentary pause on the other end of the line. Hakan hung up with a funny look on his face.

"He *laughed*. What, can he read our minds now?"

Sylvia said, "He's in California. If I were in California, I'd be laughing."

"He said if we were that desperate, we should take an afternoon off or something," Hakan said.

Sylvia didn't want to go to a conference, or even take an afternoon off; she wanted to finish. They had to be getting really, really close. Two weeks ago they had put chromosome 11 to bed, and Atakan had immediately started loading the gels for 12. They had finished the "long arm" – the larger half – and had been working on the short arm for a few days. Herbert had probably finished 14 yesterday would now have jumped to 13 – their gene had to be hiding on one of those two chromosomes.



Why couldn't the linkage region have been on chromosome 2, or 19, or at least somewhere closer to the beginning of her list, or Herbert's? Of course it would be in the last place they looked. Why hadn't they started in the middle and worked their way out?

Atakan's job was the most routine at the moment, but he never seemed to get especially bored or frustrated. Maybe she should start a fight, just to see how he would react. She was in the mood for a fight.

Every time the phone rang, she thought it would be Thomas, announcing he'd found the Holy Grail. It often was Thomas on the line, but usually just to give the next LOD score. Sylvia wrote it on the board. He always called her "Sylvie", and it drove her crazy.

Hakan had just started to spread out his paperwork when Evi put her head in the door.

"Don't you dare," she said, but in that special tone reserved for Hakan. "I have to write an e-mail."

Hakan sighed and got up. "How does she *do* that?" he asked Sylvia. "How does she always know?"

"I know everything," Evi said. The worst thing about it was, she probably did.

And then the phone rang. Sylvia picked it up and tucked it under her ear. "Sylvia Bähring."

"Syl-vie," said a voice. The first time it had happened, she had politely corrected him. After the tenth time she had realized he was doing it on purpose, and it never failed to irritate her. Now she just hung up.

"Did he call you Sylvie again?" Atakan said. She rolled her eyes. They waited.

In exactly the amount of time it had taken Thomas to redial, the phone rang again. Before she picked it up, Sylvia said: "One more time. Just one more time and I'm going to kill him." She glared at the receiver and snatched it up.

"Did we get cut off or something?" he said.

"Oh, was that you?" Sylvia asked. Innocently.

"I'm coming over. Have a look at the sections you just finished, short arm of 12." He gave her the names of the markers on either side. "I think I've got it."

He had said the same thing two weeks ago, referring to a region of the long arm they had just finished. They rushed the champagne to the fridge because Thomas' computer programs had suddenly produced an LOD score over 3 for a region on the long arm of chromosome 12.

They had called Herbert, who packed up and booked a flight out of San Francisco. A day and a night later he arrived back in Berlin, briefly stopped by his apartment, and headed for the lab. They were glad to have him back – even though they quickly discovered that the announcement had been premature; something had been overlooked.

Linking a particular region of DNA to Bilginturan's syndrome required tracking segments of DNA that had jumped from one chromosome to another when chromosomes came together as sperm and egg cells were produced in a parent. This process gave each and every reproductive cell a unique mixture of the genetic material of the parent. If those cells had received a complete, intact chromosome from each parent, and it stayed that way, you would be able to figure out that a problem was located on chromosome 12, but you wouldn't be able to zoom in any farther and determine a more precise location.

But the fact that segments jumped from one chromosome to the next meant that instead of following whole chromosomes, you followed the fragments. Their lengths told you whether they came from the mother or father. This first part of the linkage study was to inspect about

450 regions – the segments marked out by the microsatellite markers – and find one that contained the basic fragment. You didn't know which one it was, or what it contained. But you did know whether a piece from the father or mother had been the source of the fragment. The linkage analysis would show whether it matched the pedigree.

Some regions didn't contain any information, because you couldn't measure any change in length of the marker in a person who inherited the syndrome and one who didn't, at least not in every person's DNA. The mistake of a few weeks ago had happened because one such region had slipped into the calculations. When you compared this region in affected and non-affected family members, there wasn't enough information to distinguish them. That wouldn't be true if it really held the DNA for the syndrome. Sylvia caught the mistake and the champagne had stayed in the refrigerator.

All the way along, Thomas had had important support from outside the group. He was familiar with a range of computational tools used in linkage studies, but they needed to be adapted: Most of the time you didn't deal with families this large. Here it was even hard to print the pedigree on paper. To keep it readable, the scientists had to bend the traditional, tree-like form used in recording a family's structure into a circle.

Some of the tools Thomas needed were developed by Jürg Ott, a genetic statistician from Switzerland who was working at the Max Delbrück Center at the time. Ott was a world-class expert in the field who would lend some valuable help at a crucial moment: when the study was finished and the group submitted the paper to journals.

Ott went on to establish a Laboratory of Statistical Genetics at the Rockefeller University in New York. For many years he has had a second position as a visiting professor at the Institute of Psychology of the Chinese Academy of Sciences in Beijing. His website, which captures both his scientific activities and personal interests, suggests a personality who would be fun to meet. The page collects piano improvisations he recorded (think Scott Joplin, with a little irony), a list of prestigious awards he has earned; and – who could possibly resist – a link to "Swiss folk music."

This time, the hit on the short arm of chromosome 12 turned out to be the right one.

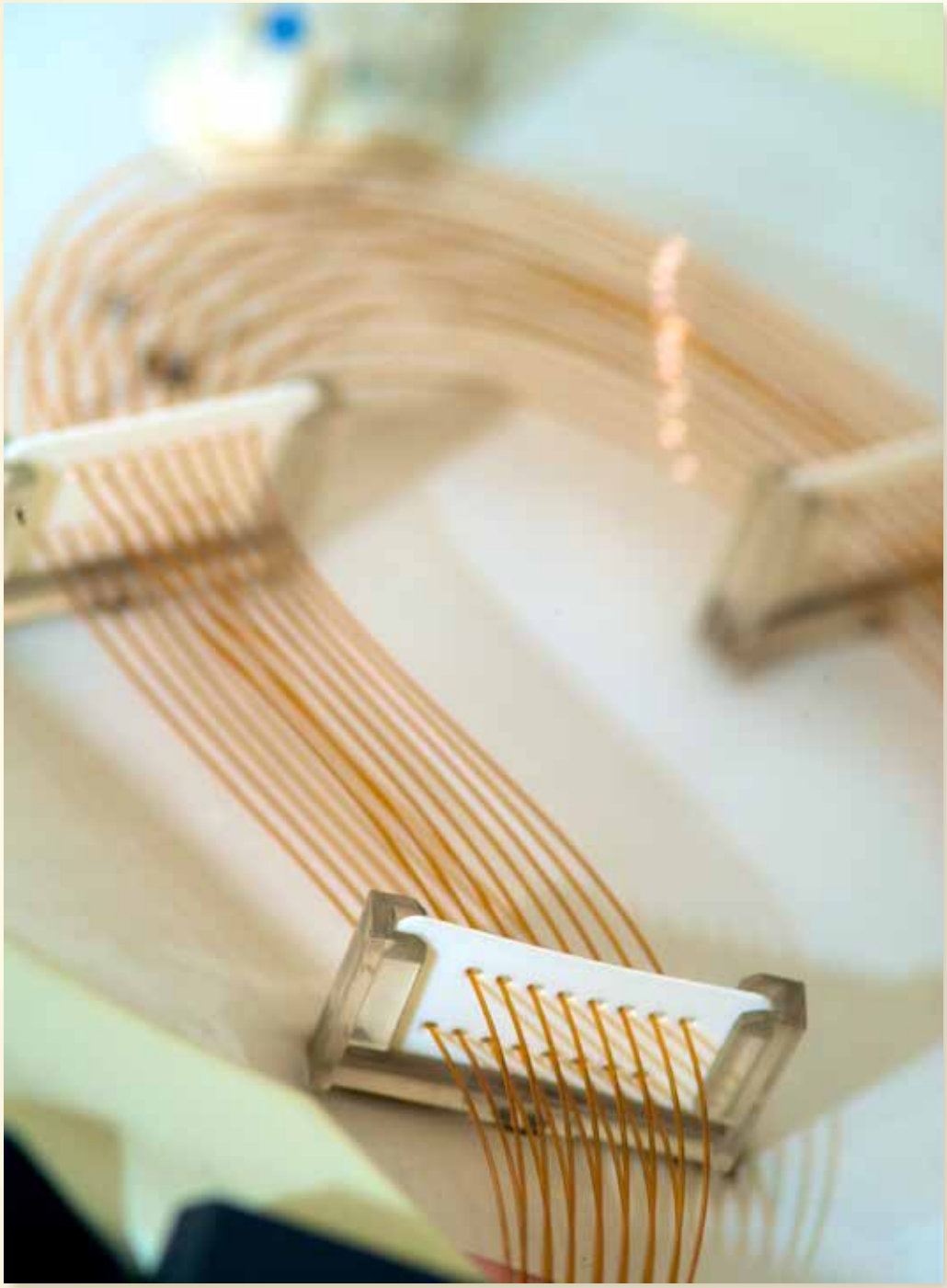
Door to door, it usually took Thomas fifteen minutes to leave his desk at the MDC, unlock his bike, and pedal over. Atakan had heard the phone and come over from the lab. He found Sylvia flipping through her results from the segment that Thomas had identified. She knew what to look for now, and didn't see anything wrong.

Today Thomas made the ride in record time. As he came into the office he was trying to keep that impassive look on his face, but she could tell he was excited. He started talking before he even got through the door, and he put a printout in front of her.

The LOD score was higher than three. In fact, Thomas said, it was 4.85. Sylvia couldn't find anything wrong with the region; it contained plenty of information. They had located the source of Bilginturan's syndrome; it was located on the short arm of chromosome 12.

Thomas went to find Fred Luft; Hakan went looking for Herbert. Sylvia picked up the phone to call Herbert, and Atakan brought out the bottle of champagne.

So about a year after the group's return from Turkey, their work had finally paid off by narrowing the region of defective DNA to a specific region of chromosome 12. This area, called the *locus*, was still very large and certainly contained many genes. Sixteen years later,



any biologist looking at a region of the genome this size would realize how vast and complex it truly is. Sylvia recently estimated that the original linkage area consisted of over 16 million base pairs and contained 78 genes, most of which could be expressed as proteins in several different forms. Today we know that even this number is an oversimplification, because DNA contains many other types of information that were unknown in the 1990s.

By the standards of 1996, finding the locus was a huge step – even if it told them nothing about the region's contents, what kind of changes it had undergone, or why those changes caused short fingers and hypertension. Eventually the region might be a gateway to answering those questions. That might take a long time, they knew, but they felt pretty good about having found the door in the first place.

Writing up the paper was a team effort. They sent it off to a prestigious journal, *Nature Genetics*, whose editor instantly turned it down. "We don't publish linkage stories anymore." They should try again, he suggested, when they understood a bit about the biology of the sequence. But Jürg Ott stepped in and asked for a reconsideration on the grounds that this was the first time a monogenic defect had been linked to essential hypertension, or something very much like it. That was important in its own right and the community should be informed. The editor changed his mind and agreed to publish the paper.

Publication in *Nature Genetics* was virtually a guarantee that Bilginturan's syndrome wouldn't vanish off the radar again for 20 more years. Fred wasn't going to let that happen anyway, but the paper would open doors. Somewhere there would be labs working on the genes within the region; their research might provide insights into the effects that a particular molecule had as cells grew into a body, shaping its organs. That might tell them where to look as they sought the physiological causes of the hypertension.

The pedigree of the Turkish family was so large that it couldn't be printed in the traditional, tree-like form; instead, the group made it round, with the ancestors in the center.

It was a great success, but the publication triggered a rift in the team that would never completely heal. When the paper was mailed off, Herbert Schuster's name appeared first in the list of authors. Although officially, Thomas and Herbert were given equal credit, every scientist who saw it would interpret this to mean that it was Herbert's project: he had initiated it, organized the work, spent the most hours on it, and probably done most of the writing. Thomas Wienker was incensed. He had found the paper in the first place, and he had carried out the analysis that gave it meaning. And he considered himself the only true human geneticist on the team.

Thomas already felt like enough of an outsider: all the others worked in the Franz-Volhard Clinic, his desk lay on the other side of town, and he didn't have his own team. In that situation it was hard enough to feel appreciated, and now he felt abandoned.

The group had already investigated one gene near the region, called PTHLH, which made a protein called the *parathyroid hormone like hormone*, before they published

the paper. PTHLH had already been shown to play a role in bone development. In March 1995, a group in Japan had published a report on experiments in rats demonstrating that the PTHLH gene was also involved in the relaxation of blood vessels. It seemed like a promising candidate for a gene that could affect human hypertension.

PTHLH had already been carefully studied by other groups, which meant that a lot was known about its DNA sequence. It contained small repeated sequences that could be used as docking points for new probes. The scientists quickly set up an experiment in which they used PCR to amplify the version of the gene found in all the family members. The first 50 segments they analyzed revealed that affected patients all had one particular variant of the gene, whereas nonaffected people had another.

"We managed all of that in one evening, and we were tremendously happy," Sylvia says. "But there were nine more people left to cover. The next day we ran those. And the very last segment we looked at – from the last of the patients – had what we thought to be the 'healthy' form. This completely ruled out the gene, and it was like a blow to the head."

Still, the paper was in, and they celebrated in Evi Jeschke's yard. Hakan picked up a large bottle of champagne and started shaking it, hard.

"Don't," Evi said, but he nudged the cork with his thumb and it went sailing across into a neighbor's yard. Okan quelled the fountain with a glass.

Herbert profited from his trip to Foster City and the publications in some ways that hadn't been foreseen. "For me personally, establishing contact with the biotech industry was an important step not only because I learned new techniques, but also had access to technologies that weren't yet accessible to other research groups. And, most of all, I became familiar with the structure of a business. The cultures of academia and industry were very different. One aspect, for example, was that businesses had a corporate identity and a culture of cooperation. Part of that was surely do to my status as an academic guest, but really every person working there would come along and say, 'Can I help you? Can I do something for you?' and then drop everything they were doing to help. Seeing this was important later when I began a business of my own."

Another unforeseeable consequence came from the fact that the group's article appeared just at the time the publishers of *Nature* were making the decision to put out an Asian version of the journal. A conference was organized for the event, and Herbert was invited to attend.

"I got to meet the Emperor of Japan," he laughs. "I was one of just a few who got to shake his hand. This happened during an evening reception for ten of us scientists from the West, from various countries. We were all incredibly impressed, particularly by the way the Japanese scientists were moved by our presence. The Emperor addressed us in English, quite informally – 'So, Mr. Schuster, how do you like it here?'

"There followed three minutes of small talk, but it's one of those things you remember forever."

Over the months since the Turkish family's stay in Berlin, Hakan gave Fred regular updates and brought along results from the clinical work as he sorted the findings from the hospital examinations into tables and charts. The tests would form the basis of his dissertation and a second paper that would be published in 1996. It shouldn't go to the journal before the linkage study had been completed and published, because Bilginturan's syndrome needed a firm genetic foundation.

But already, even though the rigorous analysis of the hospital data hadn't been completed yet, the results from the family's stay had been clear enough to establish that their problem was more like essential hypertension than anything else. It was time to start thinking about a drug trial. The question was how to get it done.

Probably the only way was as the subject of a doctoral thesis, Fred thought, and Okan was really the only feasible candidate. Hakan already had a topic, the clinical study on the family, and it shouldn't take him too long to finish it. After that he would be swept along into the next phase of his medical education: a year of clinical rotations, which required four months in internal medicine and four in surgery. He could do those two in Berlin-Buch, and then would have a four-month elective rotation that he ought to do abroad. Fred wanted to send him to Indiana, but once again, Hakan's father had firm ideas about his son's education. Mr. Toka *insisted* it be done at Harvard. That would take time to set up; Fred began working on his contacts there.

As far as the drug study was concerned, Okan had impressed Fred as someone who would probably be able to handle the project – but it would be a huge job, and he'd have to be extraordinarily motivated. The timing was about right: he would be finishing the first phase of his medical studies soon and would need to fulfill the research requirement with the thesis.

Okan appeared from time to time, whenever he had a break in Munich, and it wasn't long before he came by. Fred asked him how things were going. They talked medicine for a while: professors that they both knew, interesting cases they'd seen. Okan said that he had thought a lot about the trip they'd taken, how fascinating it had been to take part in field work, and the ten days in Berlin – providing the perfect segué into what Fred wanted to ask him. And there was no better way to bring up the topic than to just bring it up.

"If we're going to take care of these people, we need somebody to go there and stay for about a year," he said. "The point is to do a good, systematic drug study. How would you like to take it on?"

Okan looked at him. "Sounds very interesting," he said, feeling honored to be asked and at the same time not a little terrified. "I've been thinking about a topic…" He paused. "A year's a long time."

Okan was thinking about the subjects some of his friends had chosen. Most of them regarded it as a hoop to be jumped through, a formal requirement they could fill by helping out on some dull clinical study, doing statistics; they regarded it as something to get out of the way with as little pain as possible. German medical schools were full to the brim with thousands of medical students. Even if the professors had wanted to help each one develop a real project, and oversee it like it should be, it couldn't be done.

Fred was more than aware of the situation. "In Berlin we pushed 600 students per year through this system. For most the research requirement is just something annoying that they have to do, and they try to get it over with in the shortest time possible. Some of the professors are big 'clinical animals' who are, on paper, responsible for 50 doctoral students at a time. They put their students on relatively meaningless topics, have them evaluate X-rays or whatever."

The Toka brothers were allergic to the idea of doing something meaningless. Okan had listened to his brother's reports on his work with envy – the people he was meeting, the contact he had with researchers he called brilliant and who were willing to invest in their students. So Okan was completely up to date on his brother's work; Hakan talked constantly about the opportunities he'd had, and raved about working with Fred Luft and Herbert Schuster. He'd found an environment in which he could push as hard as he wanted, and it would push right back.

"You know, this is a great chance for you," Fred said. "You liked the field work; this would be better. If I were in your shoes, I'd jump at the chance. I can guarantee you that you'll never regret it; it will change your life."

"My thinking was a bit philosophical," Fred told me later. "I saw this young man with a Turkish heritage, but who had never lived there. At some point, I thought, if he were older he might regret never having confronted this aspect of his life, or what it means. I also didn't have much trust in finding a Turkish colleague that could take care of this situation. And I thought, in case we find something, if we hadn't made some effort to take care of this family, we wouldn't have carried out our ethical responsibility."

The project would also give Okan a chance to work as a real physician, Fred said, in a way that very few medical students could accomplish. The family wasn't receiving primary care. He would have to take care of that as well.

Okan didn't have to decide this instant; he wanted to discuss it with Hakan. But before he left Berlin, he had made up his mind. He paid another visit to Fred and said, "Okay, I'll try. I don't know if I'll be successful, but I'll do my best."

Another thing that kept coming to Fred's mind was his encounter of a few years back with Ramin Naraghi in Erlangen. At the time, Fred had dug into the literature to get an impression of Peter Jannetta's hypothesis. He was more impressed by the work on facial neuralgia than the evidence on hypertension work; what had been collected so far wasn't sufficient. He also had a natural skepticism of scientific zeal, and Jannetta had plenty of that.

But Ramin's successes at predicting hypertension from brain scans seemed to be pretty good. Cafer's family could serve as a proving ground for the hypothesis. It wouldn't hurt to take a look at the blood vessels in Bilginturan's syndrome – a session in an MRI machine was a lot more comfortable than some of the procedures the family had been through in Berlin.

So far no other physiological explanation had been offered for the family's high blood pressure. Finding a gene in the linkage region might certainly provide an important clue; until then, a look at the brain might provide sharper insights into the phenotype. The work could probably be done in the hospital at Trabzon, and at worst, they'd be out the cost of a trip. Like every action so far, arranging it would probably require some creative financing.

Ramin was still in Erlangen and had kept the collaboration with the nephrologists going. "Professor Luft had moved to Berlin in 1992, and had been gone for almost four years," Ramin says. "As far as I knew, our project was the farthest thing from his mind. Then one day out of the blue he called up and asked if I wanted to work on a project involving looped vessels and hypertension. It was completely unexpected, but I was overjoyed. I said, 'Right away! Where?' And it turned out to be Turkey."

The acceptance of the paper gave them a boost at a time when they knew they would soon have go through exactly the same process of sequencing and analysis all over again. The region they had identified was vast; it might contain hundreds of genes, which meant it had to be narrowed down. That meant carrying out the same procedure within this precise region that had been performed on the entire genome. It sounded simpler, because the region was smaller, but it wouldn't be. The workflow would be the same, and was likely to take even longer than the first analysis required. In that case they had been able to draw on ABI's markers, which had already existed or were being developed.

Now they were breaking new ground. ABI and the scientists in Fred's group would have to peer into the region and find more subtle patterns in the DNA sequences that the dyes could be attached to. The smaller the region, the less likely you were to find fragments that had been shuffled around as hereditary material was passed from parents to their children. Developing the new markers would take a long time. And the team would now add 19 more members of the family to the study.

Sylvia and Atakan and their colleagues started in on the new material from ABI. Making the probes took longer than it had the first time around. They had to be custom-built, based on "primer" sequences within the short arm of chromosome 12 that were proprietary information of the company. They were essential in starting the PCR reactions and generate the DNA fragments.

ABI had been providing dyes of three colors, which meant that about ten different fragments could be run through the sequencer gel at about the same time. Now the group had to work with single markers, and work harder to make the primers work properly for the PCR reaction.

As the markers were established within the region, Atakan went back to his routine with the PCR machine, the pipetting, and the sequencer. Sylvia added more notebooks of data to her shelves as she turned the data into numbers and sent them by e-mail to Thomas. Once again, the statistical programs had to be adjusted to cope.

The effort took the group well into the next year. By the time they finished, they had reduced the size of the linkage region by more than half. This would eliminate a lot of genes and sequences that had to be considered.

Establishing linkage in a smaller area would require adding family members – everything depended on finding segments that had jumped between chromosomes. Ideally, breaks could be found very close to the two ends of the damaged DNA that caused the syndrome. The best chance of that happening was to add more people to the study. But the coverage of the Turkish family was almost complete.

Well, maybe they could find other people who had suffered mutations or other types of damage on chromosome 12, even if the individuals weren't related to the Turkish family. The entire group was constantly on the alert for new studies that were being published on the topics of short fingers, hypertension, and particularly their linkage region.

Sylvia came across a report about a five-year-old Japanese boy who was entirely lacking a segment of his 12th chromosome – he had short stature and fingers and, they discovered later, borderline hypertension if you took his age into account. What was particularly interesting was that his short fingers had the cone-shaped epiphyses that were particular to type E brachydachtyly.

Sylvia immediately wrote to the author of the article, Toshiro Nagai of the Tokyo Metropolitan Children's Hospital. Nagai was extremely cooperative, and promptly mailed her samples of DNA from the boy, his parents, and his siblings.

The analysis of the material showed that the deletion had affected part – but not all – of the segment that the team in Berlin had found. A neighboring region, outside the group's focus, was also missing.

Purely theoretically, some of the boy's problems might have stemmed from the loss of the neighboring DNA. But, as Fred points out, "We thought it highly unlikely that you'd have neighboring genes responsible for exactly the same symptoms."

So far the fine-resolution work had reduced the critical region of chromosome 12 by half; with the new breakpoint in hand, the information from the Japanese boy reduced it by half again. The group had now shrunk the region they needed to investigate to a fourth of the original size.

14 A year in Provence

Okan Toka was cold, wet, hungry, and tired to the bone. Coming into the Trabzon airport late on a Friday night should have felt like a relief, but it had been a hard week, and he still had to collect his bags and load the car and drive for an hour – providing it started – until he reached his apartment. Which would be freezing cold until he got a fire lit in the coal stove and dried off. Then he'd have to stow the samples, sort the paperwork into the right folders, and take a few notes before he could fall into bed and sleep like a dead man.

That might not be so easy, either. It was hard to remember his departure 12 days ago, but it was entirely possible he had left his bed piled under a heap of extra supplies and boxes. Or perhaps he was thinking of the last time he left. Or the time before that.

It was all running together in his head.

Maybe, instead of unpacking and organizing, he'd just lie on the floor and drink something and pass out. Just lie there the whole two days until he had to start the whole trip all over again.

Come to think of it, he probably didn't have anything to drink in the house, either. He remembered writing a note to himself, BUY ALCOHOL IN ISTANBUL, but maybe that had also been last time.

Recently he'd been replaying the conversation he'd had with Fred Luft in the office that day over and over in his mind, rewriting it, giving himself new lines like, "Are you completely out of your mind?"

It seemed like the conversation had taken place about five years ago. He couldn't quite remember what Fred looked like. Maybe it *had* been five years ago. Maybe they'd forgotten all about him and left him here, and he'd lost track of time and had been doing this for five years.

Every two weeks saw this return to the airport at Trabzon, at the same time on a Friday night, when it seemed to take them hours to unload the plane. Tonight, he couldn't believe it, his bag was the very first out of the chute. He grabbed it by the heavy straps and eased it off the conveyor belt.

He was walking and trying to remember where he had parked his car when two men suddenly blocked the exit. He was so startled he almost dropped the bag. He opened his mouth and suddenly realized who they were: Mehmet, and Cafer, as big as life – well, Cafer was; Mehmet was about half as big as life. And they had broad grins on their faces. He could have cried.

"Give me your bag," Mehmet said.

Okan surrendered it and followed them to the exit. They had brought another car; Mehmet would drive, and Cafer would follow in Okan's car to take him to the room he had in the house of one of the cousins.

Later he found out that Cafer had talked to one of the last relatives he had seen, who said that Okan looked utterly exhausted after 11 straight days on the road. Okan had arrived in Istanbul from Bursa, where a child had had a fever, and the young doctor had been up most of the night. After three hours of sleep he had dragged himself out of bed and caught the bus and then the ferry to Istanbul.

"Since I was late, there was a long line to get on the ferry," Okan said. "I was sitting on the bus, which they would just drive onto the boat, but the line was so long I missed the first one and it looked like I'd miss at least one more as well. I went to the driver and told him, 'We have a problem; I can't wait.'" He had blood samples on ice that had to be delivered to the hospital right away.

At the beginning of the line stood another bus from the same company. "Come with me," the driver said, and walked with Okan past the line of cars. He knocked on the window of the second bus. "This doctor has to get to Istanbul, and he has a ticket for my bus; can he switch and get on board?"

"Of course," the new driver said. It was another example of those small bits of help that would come at the right moment to solve a small problem that could have expanded into a major disaster. Without such moments of kindness, and a willingness to bend the rules, Okan says he never would have survived the year.

Cafer, who had enough to worry about, had taken on Okan as another of his burdens.

"You look tired, my friend," Cafer said.

"Five minutes ago I was dying," Okan told him. "But I'm much better now."

His departure from Germany, months ago, had been marked by a touching send-off. Everyone gave him a present, often something practical that he might need. Herbert Schuster presented him with an enormous reference book called *Paradigms in Internal Medicine* that he would refer to whenever someone in the family required medical attention. Fred Luft gave him his stethoscope. "It had its name on it; it was old and used, and I still have it," Okan says. "I'm still using it 15 years later."

Okan had never lived in Turkey before; his only trips to the country, aside from the field expedition, had been vacations with his parents or brother. The destination was usually Istanbul, where they had friends, or occasionally they visited his father's hometown in the East. He had very little experience with the "system"; at least his language skills were good. There was a lot of vocabulary to learn – words he'd never needed – and the family's dialect took some getting used to, but he picked it up quickly.

Herbert and Hakan had come along the first week to help him settle in. "I had a lot of equipment to deal with and keep organized, and huge responsibilities. Herbert helped me look for apartments, but we couldn't find anything good." Finally he heard about an apartment belonging to one of the family's relatives in a town on the coast and moved in there.

Now he needed a car. "It's hard to write a car into a grant application," Fred says. "They don't have a category for that."

The funding from Astra Zeneca came to the rescue. Cafer recommended buying a new car; you could get a good price on the vehicle and guarantee in Turkey. Okan would need something absolutely reliable, he said. One of his regular trips would be an hour-and-a-half drive from Trabzon into the mountains, and from there he would have to drive off-road from house to house. Okan wrote to Fred, who was at first hesitant.

"I don't know, giving a young guy a new car that he'll drive across the mountains and the countryside? Can this turn out good?" Fred remembered his trip to the Yayla in the jeep. But he gave in.

Herbert and Hakan found a grey sedan that Okan used when he was on the Black Sea coast to take him from his apartment to the village and the homes of families in the area. By the end of the year he would log more than 30,000 miles: hard miles, mostly off-road.

When Fred visited half a year later, Okan says, he inspected the car with critical eyes. Later, over a glass of wine, he said, "I was surprised to see the car was still in such good shape. Guess it was a good idea to buy a new one after all."

Before leaving Germany, with Fred's help, Okan worked hard to create a master plan for the year that would involve trying to get the family's hypertension under control. Okan would test the effects of five drugs that were commonly prescribed for hypertension and would be provided by the Astra-Hässle Corporation, at the time Astra Zeneca, which has continued to provide drugs for the patients over many years.

The initial contact was established by Herbert and Fred. Okan and Hakan were given the task of working out the details with the company. They drove from Berlin to Hamburg to present the idea for the study to high-ranking members of the company's management. They gave a presentation on Bilginturan's syndrome and the group's research.

"Here we were, two medical students, presenting the project and a major proposal for a drug study, using first-line antihypertensive medications that Astra Zeneca produced," Hakan says. "We told them we needed a pharmaceutical company to supply drugs for a placebo-controlled, double-blind study. We were pretty nervous. They'd need to prepare the drugs in a way that Okan and the study participants couldn't determine which one was which. Well, they agreed to help, and they even gave Okan some important tips on how to carry out the study itself."

The list of drugs included diuretics, beta blockers, alpha blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors. At the end of Okan's stay a sixth drug was added, an imidazoline receptor agonist

moxonidine. Each had been developed to control a distinct biological process related to blood pressure.

One hurdle to be crossed – which took a considerable amount of effort and has continued to be an issue for the project – was the difficulty of doing medical research on human subjects across international borders. In Turkey the project had to be approved by an internal review board at the University of Hacettepe. In Germany approval was received by a similar board at Humboldt University, in Berlin. Then all the potential participants had to read and sign a consent form in Turkish.

The paper that eventually came out of Okan's work describes what he did as a "randomized, cross-over, placebo-controlled, double-blind trial." In other words, Okan would administer a drug, measuring its effects on blood pressure and other aspects of a subject's health over four weeks. Then the treatment would be stopped for two weeks, to flush the drug out of the person's system. Then he would start the next drug.

Patients suffering from essential hypertension in Europe are often treated with multiple drugs. Depending on the individual, each may have a mild effect; combining them often has an additive effect that lowers hypertension to acceptable levels. "Originally, in this case, we thought that we might be able to find a single drug that worked on everyone," Herbert says. "Only a single gene – therefore a single mechanism – seemed to be responsible. That suggested that one treatment might be more effective than all of the others combined."

"There are several examples in the literature of one drug working particularly well for a specific form of hypertension," Hakan says. "A drug called amiloride, for example, is rarely used to treat high blood pressure because it's a very weak diuretic. But if you use it to treat people with a condition called Liddle's syndrome, it can normalize patients' blood pressure on its own." The reason has to do with the nature of their genetic problem: People with Liddle's syndrome have an overactive sodium channel in the kidney, and their blood pressure reacts very strongly to salt. In this case, even combinations of drugs can't get the hypertension under control. But amiloride works.

At no time was Okan or the patient allowed to know what drug was being tested, or whether a placebo (which looked like a drug, but had no active pharmaceutical substances) was being used. This is standard procedure in a clinical trial. A physician's expectations can influence what he sees in his data and how he interprets it, and so do a patient's. The most well-known result is the placebo effect, in which a patient's health improves simply because he or she believes that an effective medication has been administered. Scientists still don't know why this happens, but placebos are crucial controls in every drug study.

So being left in the dark was necessary, but it made things complicated for Okan, because he still had to keep all the drugs organized and apply the right one at the right time. All the packages were coded and labeled, but he was giving different family members different drugs at the same time; after four weeks he stopped so that their bodies could rid themselves of the substance, and then he rotated to new treatments. It required perfect organization and record-keeping. If he couldn't reconstruct one of the steps later, the data would have to be thrown out.

The study began with 17 patients. He had to see each one every two weeks. Each visit would require measuring blood pressure regularly for a 24-hour period. If the person had to work, he had to wear the cuff attached to a small monitor on his belt.

He had to take blood and urine samples and try to detect the effects – possibly adverse reactions – of the medications that were being tried.

One 28-year-old complained of dizziness and lightheadedness during the very first phase and requested that her therapy be stopped; Okan called Herbert, who

The mayor, Okan and Mehmet

checked the drug schedule. She had been taking the placebo. The woman agreed to rejoin the study and completed the rest of the program successfully, but they didn't include her data in the final results. Three more women decided to get married, and would likely get pregnant, so they dropped out as well. And one man was unable to stay in for the last treatment, which involved the new drug that had been added late. At that point only the single medication was being tested, which made things easier on Okan.

At the end of the year, Herbert and Okan worked up the results and discovered that four of the drugs had a significant effect in lowering the family's blood pressure. Although they didn't find a single substance that would work on its own, using a beta blocker in combination with another drug usually lowered their hypertension to survivable levels.

Ever since, Okan, Hakan, and Fred Luft have found "creative" ways to keep the family supplied with drugs. Very few of the family members could afford health insurance sufficient to pay for them – those who could were usually already being treated by their doctors – but Astra Zeneca has generously continued to provide the family's drugs for free. As a result, they have made a major contribution to the survival and health of many family members.

Delivering them across the border usually hasn't been a problem, provided that the brothers take them over in person. "We go armed with letters from the company and Humboldt University that explains the purpose of the drugs and stating that there is no financial gain," Hakan says. "Sometimes we've had a letter from officials in Ankara as well. We have almost always encountered good will on the part of Turkish customs. It's only been a problem when we have tried to send medications through the mail."

While Hakan made some of these first trips, Okan has managed the deliveries since his brother moved to the States. They admit that it's always an issue to provide drugs without a close monitoring of their use, but by now most family members have contact with a physician who oversees their treatment.

And the main point is that in the nearly twenty years that have passed since the "German doctors" arrived, not a patient has died from a stroke. "Only two have died at all," Okan says, "and those were older people who had already had strokes and were too far along in the progress of their disease by the time we reached them."

One of the aspects of life that struck Okan the most during the year was his encounter with poverty. "By German standards of comparison, and even those in Turkey, most of the people I saw on a regular basis lived in very poor circumstances. They usually had no steady supply of warm water, heat, or power. It might not be too obvious during a short visit, but if you see them regularly, over time, and watch the problems that you have, it has an effect on you. I didn't just visit to take their blood and measure blood pressure; it was important to take care of the whole person and all the issues they had."

One woman badly needed hip surgery but was unable to afford it; Okan worked with others in the family to arrange it. "What is very special about these people is that they are a family; once they accept you, you are a member of it and you are involved. If you see something happening, you have to do something."

One serious incident involved a case of accidental poisoning. "A woman had smeared her two children with a salve they normally used for their cows, and the children were poisoned. They called me and I had to drive the children to the hospital. There was an antitoxin available, but

basically they just gave the kids fluids and they turned out all right."

Another person had such severe stomach problems that Okan took her to the hospital for an endoscopy. The problem turned out to be an advanced case of stomach cancer that eventually claimed the patient's life.

Wherever he went, the family greeted him warmly; whatever they had, they shared. Even when they didn't have much to eat, they offered him cheese and black tea and hoped he would stay and join them. "In spite of the hardships, they enjoyed their lives. They didn't need much more. They were happy."

And some of them went far out of their way to help. "One affected older lady made a trip by herself, every fourteen days, of 300 kilometers by bus to let me take blood and administer the drugs. She spent the night with a relative and went home the next day, another 300 kilometers."

Most of Okan's patients lived in the vicinity of the village on the Black Sea coast. "But others were scattered all over Turkey: in Istanbul, a city south of there called Bursa, and Ankara, in the middle of the country. It took me about a week to see all the patients in the mountain villages on the coast, which meant driving from one to the next, off-road, in my car. After that I usually went to Istanbul, then on to Bursa, and ended my rounds in Ankara before flying back to the coast."

But the blood samples he collected had to be frozen and preserved, which meant constant flying back and forth from each of the locations to Istanbul to deliver them on time. "I took samples from the Black Sea coast to the lab in Istanbul, and the samples from Ankara and Bursa to Istanbul, and then back to the Black Sea. The blood samples were a continual problem. You had to freeze them down to 20 degrees, and that was a problem."

To handle them on the Black Sea coast, he had to find dry ice. He found a producer who made deliveries in Istanbul and went to talk to him. The man asked him how much he needed. When Okan answered that one or two kilograms would suffice, the man was startled. "Normally they sell it by the ton," Okan says. "So we had to figure out a price for such a small quantity, and agreed on a sort of symbolic rate for packing and sending it by train. Once we had things worked out, the procedure went smoothly the whole year."

Every once in a while the electricity went out in Okan's apartment, making him worried about the blood. "You couldn't do much except hope that it would come back on in an hour or two. Once it had been over two hours, and I got worried, so I called Cafer. He called the power company and said sternly, 'We have an important doctor here, and he has blood samples, and he needs his electricity!' The man on the line told him it would be another hour, and then, thankfully, it came back on."

Cafer was an invaluable help. Okan spent a lot of time with his immediate family, and in the Hoca, he found an educated man, a friend with whom he could talk, someone to check up on him regularly and help out with problems. Cafer managed this in spite of his many responsibilities as the religious leader of the community. A requirement for his position was a university degree; as a young man he had gone off to study the Islamic religion then had come back to his home community to step into his father's shoes.

One thing he accomplished was to arrange for the building of a new mosque; Okan said that he and the other scientists made donations as a sort of "thank you" for the contributions the family had made to their work. The community had already obtained a lot of funding, and the researchers couldn't add much, but it was another way of showing that they could give something back.

Cafer had a television, and sometimes when Okan would show up, there would be a dozen people or more gathered in the living room, sitting placidly around in a huge circle, nothing moving except their eyes. "They would watch the news, sports, talk shows… They found it hilarious to see these crazy rich people on the screen, what they do and talk about, and they would sit around commenting on it."

It was a time when technology was moving into the villagers' lives, bringing benefits but also quick changes. He watched Cafer try to keep the balance. Companies had bought some of the hazelnut farms – so far, not from the family – but there was also a new plant to process the nuts, offering jobs and raising the standard of living in towns a bit closer to the coast. Overall, it was a positive trend, but Cafer was aware that it might wipe out their way of life.

One of his roles was to settle disputes. "The bigger the family, the more the problems," Okan says, and Cafer had a very big family. "Disputes arise about money, and it's the job of the Hoca to settle them. Sharing, not sharing… Often it's simple things. Relatives might argue and then stop talking to each other, and he tried to step in and smooth things out."

Hakan called often, to lend moral support and check up on his younger brother. "I was really worried about him, especially at first," he says. "Life over there was nothing at all like the way we had grown up. Okan did a phenomenal job planning the whole thing, educating himself about drug trials, and keeping organized the whole time.

"When we went over to help him get settled in, it was winter. He lived in a village with no gas heat – just a small coal oven. There were no pubs where he could go get a beer and watch sports, or do the things you need just to take a break."

So Hakan was worried. "Are you sure you'll be all right?" he asked.

"Sure," Okan said, but his brother knew he was worried as well.

In the summer and late autumn some of the family members were up in the Yayla, and Okan had to make the same long drive that Fred and Hakan had made during the very first visit: up tracks that were little more than footpaths, evading stones, driving across small streams. He didn't dare take a look at the undercarriage of the car, but he constantly checked the ground where he parked for signs of oil leaks.

He had to carry out the 24-hour blood pressure measurements even in the mountains, and one time he finished late. The family told him to stay overnight – descent in the dark would be dangerous because of snow and animals; he might encounter wild boars. But there was a tight schedule. Mehmet decided to go with him, and he brought along his gun. Half-way down the mountain, after midnight, in the middle of nowhere, Okan suddenly had a flat tire.

"I had to change the tire, and Mehmet stood there with a flashlight in one hand and a gun in the other. And yes, wouldn't you know, we suddenly heard a noise – a herd of wild pigs had come out of the woods and were curious, snorting and moving about nearby. Mehmet was afraid of an attack; I was mostly worried about the precious blood sample I had just obtained. He fired a shot and scared the pigs away. I finally got the tire changed and we could continue on down the mountain."

Okan's involvement in the family's life often required him to do things beyond just medical care.

Ali and Okan

When harvest time came, all hands were needed for the job, which lasted about 25 days. On one occasion this fell just at the moment he needed to take a critical measurement. It was the end of a four-week trial of one of the drugs, and getting data from the patient who was supposed to work was crucial.

"I tried to explain how important this was," Okan says. "But they have priorities, and my patient said, 'Sorry, I am needed, I have to go to the harvest.' I knew that if he worked all day, it would completely skew the measurements I would be taking. He really had to stay at home and not do any work.

"The only possible solution was to get somebody to go for him – and since there was nobody else, that had to be me. I told him, 'Okay, you stay here, and I'll go do your work for the day. But you have to promise to measure your blood pressure the whole day.'"

Okan went out with the others, who showed him where to pick up baskets to collect the nuts. The trees lie on a slope and are small – usually rising only two or three meters. The farmers go from tree to tree, picking up the hazelnuts from the ground or sometimes climbing onto the first branch of one of the trees.

Okan followed along, watching what the others did and trying his best. "I had no experience compared to these professionals, who have been doing this their whole lives. My baskets weren't nearly as full. But it was fun."

15 The short-fingered musketeer

Ali's house lies a few kilometers from Cafer's, tucked into a niche in the hills. Today he is the oldest living male with Bilginturan's syndrome, having outlived Kemal and his other affected brothers by nearly two decades. He was in on one of Kemal's first trips, leaving a trace in the medical literature that stretches back farther than Bilginturan's study: His photograph appears in the second paper ever to mention the family, written by Mithat Veysoglu of the hospital at Samsun.

"Ali has been engaged in this scientific project very deeply for a long time, knows a lot of doctors, and he likes to talk!" Okan says. "He's always gone his own way and has had a mind of his own. As one of the oldest men, he is a central figure in the family, and sometimes people aren't really sure whether they should listen to him or Cafer, because they don't always agree. Ali is a sweet, friendly man, about five feet tall, and he wears huge glasses. He's a man of strong faith, and he also has his opinions, and occasionally that has brought him into conflict with his neighbors and the rest of the family."

Ali has health insurance and can afford his own drugs, Okan says, which probably explains his survival – his doctors began treating him for hypertension early on.

He has made sure that his four children are integrated into society. Three of them are affected by the syndrome. At least two of the boys have attended the university. One of the girls, who was 12 or 13 when he started his drug study, continually asked questions about what Okan was doing. She went on to become a nurse.

One incident that occurred during Okan's drug study almost ended up costing Ali his life – and it inspired the title of this book.

Okan was making the rounds of his patients in the village when he got a frantic call from Ali's son. He never exactly figured out what had set things off, but for some reason an argument broke out with some neighbors who had come onto Ali's land. Things escalated to the point that Ali went inside, brought out an old musket he had inherited from his grandfather, and fired it into the air. The troublemakers scattered, and Ali thought, "That's that."

Well, it wasn't "that". When the neighbors got home, they called the police, and a district police car came up from one of the towns to investigate what had happened – or at least to quiet things down.

Ali saw the car coming up the road and immediately knew what it meant. "He wasn't afraid of the police," Okan says, "because he had the right to defend his land and scare people away. The problem was that he didn't have a license for the gun."

He frantically sought a place to hide it, but by this time the police were knocking on the door. In the heat of the moment, he simply threw it out the window. It didn't take the police long to find it, and their next request, of course, was to see his license. He couldn't produce it, so they packed him into the car and drove him away. By the time Okan found out about the incident, they had him in the district jail.

Ali's wife was in tears. Okan got the story from the son, who begged him to use his influence as the family doctor to get his father out of prison. Okan immediately drove down to the jail and asked to see Ali. "I visited the scared old man," Okan says. "He told me the story all over again, protesting that the neighbors had been bothering him; he'd just wanted to scare them away and hadn't done anything wrong."

Okan spoke to the police officers in the station. He asked what the charges were and what sort of punishment Ali should expect. The officers were polite but firm. Things looked pretty bad, they said. Using an unlicensed gun was a serious offense; too many people in the countryside had them, and things could easily get out of hand. The justice department's attitude was quite strict. In any case, the old man would probably be in jail for two or three months until he could be brought to trial.

Okan was stunned. Without his medications, and in the stressful environment of a jail, Ali was effectively being handed a death sentence for a minor offense.

He tried to explain the situation to the officers, but their hands were tied. "They told me the only thing I could do was talk to the district attorney, who was responsible for establishing the charges and prosecuting the case."

Okan didn't get anywhere with the district attorney. He was invited in and sat on the edge of his chair and tried to explain the situation. The man ordered tea and invited him to drink while he made a phone call. He spoke to the police officers and hung up the phone.

"Ali is an honest person," Okan said. "I can promise you that he won't run away; he lives here and has family here and is too sick. He'll appear for the trial. But the most important thing is that he has a congenital heart disease and high blood pressure that is very severe."

The attorney shrugged and said there was nothing he could do.

"He has already had one heart attack," Okan went on, "and from a medical point of view, the stress of being in jail will surely kill him."

He was sorry, the attorney repeated, but the matter was out of his hands. "The only thing you can do is speak to the judge. Perhaps he can do something."

So now the scene was repeated before the judge, who also ordered tea.

Okan told the story one more time. The judge sipped his tea and didn't seem impressed. Okan sensed he wasn't getting anywhere and started to get desperate.

"By this time, I'd really convinced myself that Ali was going to die," he says. "I was willing to do anything. I promised I would vouch for the old man, and that I would write a full medical report for his superiors in Ankara. I'd testify that the old man was too ill to be in prison."

The judge sipped his tea.

"Then I started dropping names. I said that Ali was part of an important collaboration between the famous Hacettepe University Hospital in Ankara and the famous Max Delbrück Center for Molecular Medicine in Berlin, in Germany, and that the money was coming from the Department of Health in Ankara. I said that Ali was a key subject in our study, and without him it would probably fail."

The judge didn't appear much more interested, but he asked: "What is it that you are studying?"

Okan told him that they were trying to discover something important about the genetic mechanisms behind essential hypertension, a common disease worldwide. "It kills many, many Turkish people," he said, laying it on a bit thick, but he didn't know what else to do. "This research may be our only chance."

That, Okan says, finally got the judge's attention.

"My mother-in-law suffered a heart attack from hypertension," he said. "The doctors told us there was nothing we could do. What is all this about high blood pressure? Why don't you have a cure for it?"

"I began to talk about essential and secondary hypertension," Okan says. "I told him that Ali belonged to a very special family – probably the only one in the world – whose genes might help us understand why people get the disease."

That interested the judge as well. He asked if the problem could be inherited.

"Maybe he was thinking about his wife," Okan says. "I told him that yes, in some cases, we thought so – not just in this family. He should have his wife see a doctor because now there were good drugs to treat hypertension. I told him we were trying to find the gene, and if we succeeded, what we learned from Ali and his family might one day help us develop a cure."

The judge ordered more tea and asked more questions.

"We sat and talked for at least an hour," Okan says. "At the end, he stood up and assured me that I would have his full support for the drug study. And he would entrust the old man to my care. He used the phone to issue an order, and then I drove back to the prison.

"The old man was so excited and grateful to leave the prison he was in tears," Okan says. "He told everybody in the clan that the 'German doctor' could do miracles, even to the extent of managing his release from jail. After that I wasn't the 'foreign investigator' anymore. I was adopted, and from then on they regarded me as a respected member of the family."

On a Friday afternoon in summer, Okan was still off in Istanbul, or Ankara, or Barsun, or racking

up frequent flier miles in transit somewhere between. The Mehmet-and-Cafer shuttle service was underway on their trip to the airport in Trabzon to pick up another load of researchers from Germany.

This time the group included Fred, Herbert, and Hakan – who was dying to see his brother again – and Ramin Naraghi. As always, what they intended to do would require participation from the family members. And originally Fred and his colleagues thought they'd have equally enthusiastic support from the university clinic in Trabzon. In the latter case, despite months of communication and assurances from the university, they were about to be sorely disappointed.

The work they had planned was scheduled over three or four weekends, and its goal was to give Ramin an opportunity to test the hypothesis that he and Peter Jannetta had developed about the roles of a blood vessel and a nerve compressing the lower brainstem and a nerve in producing hypertension. In case after case, he had discovered a particular artery in the brainstem of hypertension patients which looped around a nerve, presumably compressing and overstimulating it. For five years Ramin had continued working on the idea in Erlangen. The team kept managing, with considerable success, to detect such contacts between the vessels, the brainstem and the cranial nerves using MRI. He didn't find the same situation in patients with normal blood pressure: Their vessels lay alongside the nerve, usually without much contact with it, or at least not in such a way that the nerve would be pinched.

There were three ways to test the hypothesis: one was to use an MRI machine to make images of a person's brain and, based on the arrangement of the artery and nerve, accurately predict whether they suffered from hypertension. The second was to perform an operation on a person with the nerve problem and observe that you lowered their hypertension. And finally you could carry out an experiment that was only ethically thinkable in animals: the procedure Jannetta had used with baboons, inserting a vessel-like balloon into the brainstem, inflating it, and watching the animal's blood pressure rise.

Ramin wasn't going to perform any surgery, but the clinic in Trabzon had an MRI machine. Fred had activated his funding network again to pull in money for the trip. The patchwork of funding came from the German Ministry of Research and Education, again the United States Air Force, and Astra Hässle Pharmaceuticals – who had provided Okan's drugs.

"When we went to Turkey," Ramin says, "we had a whole plan that Fred Luft had worked out to permit us to take the necessary measurements. The head of radiology at the hospital had promised to be on hand. All the doors would be open; interns would be ready and waiting; the machines would be running. Everything would be ready so that the minute we arrived, we could start to work."

Things turned out a bit differently. There was no red carpet or brass band, nor a chief of radiology or any interns. And the door was locked.

They looked at each other.

"Well, we knocked," Ramin says. "And the only person around on a Friday afternoon was a single technician who was responsible for the MRI machine. To say the least, we were slightly upset. Fred made a few remarks about the Turkish hospital system that were quite colorful and I will not repeat."

As things turned out, they were about to discover that they'd had an enormous piece of luck. If they could have had their choice of only one person to deal with from the hospital – perhaps from the entire country – they could never have chosen anyone better than this. "He was worth his weight in gold," Ramin says. He thinks for a moment. "Perhaps even platinum, or diamonds, or something."

Not yet knowing this, they entered – "rather glumly" – and inspected the MRI machine. The first surprise, which probably shouldn't have been one, was the state of the instrument. "It has tanks of chemicals that are used in developing the images," Ramin says. "When we ran a test image, what emerged was a disaster. The chemicals probably hadn't been changed in six months; maybe they'd never been changed at all."

He threw up his hands in despair, and Hakan translated for the technician. Then translated back: "He says it's no problem." And the man scurried off to find the chemicals, came back, and replaced them.

The next problem was attuning the machine to the different "sequences" it needed to highlight vessels and nerves. This was a highly technical issue that varied from machine to machine and required a delicate touch.

For that they probably needed an experienced physician, and after a lot of calling around, they finally managed to get one on site. The man who arrived certainly looked like a physician – now that they had adjusted their expectations to fit the cultural context. He wore an impeccable suit and tie, and was followed around by an assistant who was probably ready to produce black tea at any instant.

But when it came to the instrument, he was hopeless. He didn't know that the chemicals needed to be changed, had no clue as to what sequences were needed, or any idea of how to load them into the machine. But he would see what he would do.

The technician was saying something. "I think this guy can help," Hakan said.

Once Ramin, speaking through Hakan, explained what they needed, the technician said he understood and could help. He knew, for example, that the machine didn't have one of the necessary sequences. But he knew how to get it.

The MRI instrument had been built by General Electric and somehow, in spite of the hour on a Friday afternoon, the technician got one of their representatives on the phone. He would leave Ankara immediately and come.

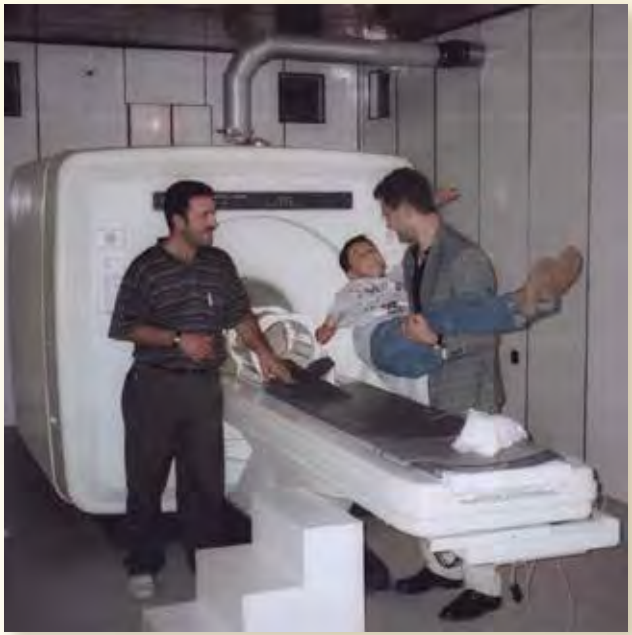
"Our technician couldn't speak a word of English," Ramin says. "But once Hakan had explained what was going on, he seemed to know what we needed before we did. He knew the machine like the back of his hand. He knew all the tricks, all the details, and managed to instantly solve any problem that we ran into. He even understood the reasons for what we were trying to do."

By this time Ramin had been digging through the user manuals for hours. Although he had been doing MRI studies for years, it would have taken him a long time to get things running – if he managed at all. Now he was stunned. "Where did you learn all of this?" he asked. "You can't read English; there's no way you can read the manuals for the machine."

The technician said that he'd learned it all just by watching people use the instrument. And one time the technician from GE had come, and let him watch over his shoulder as he worked on the machine. He'd also observed the physicians as they worked with it, learning what to do, how to do it, and why they needed it. Things had reached the point that when the doctors came with their patients, they didn't even need to explain what they needed. Now the technician asked the patients a few questions himself and carried out the proper investigations.

"This man saved us over and over," Ramin says. "He was able to produce images of such a high quality that we could achieve exactly what we wanted. Without him, the whole thing would probably have been a complete waste of time."

During those weekends, Ramin got the man's whole story. The technician was a native of the region, from a



Top left: Hakan, Ramin, Okan.
Top right: the technician stands by as Hakan helps a boy into the MRI machine. Bottom: Ramin

small village nearby – at one point he even took the scientists there. His childhood dream had been to become a doctor, but as the oldest son in the family he had had to start working early to support his mothers, sisters, and brothers. Well, he'd certainly made a niche for himself; anyone who worked with him tried to buy him and take him with them. He had received magnificent offers from southern Turkey, on the Mediterranean, where all the physicians wanted to go. It was beautiful there, and they'd asked him to come and set up – even direct – their MRI facilities. It would have been a huge step upward in pay, and Ramin asked why he had never left.

The man shrugged. "My people are here," he said. "If I leave, there won't be anyone to take care of them, and they need the kind of examinations I can do. Usually they can't afford it. So I come in on the weekend and just do it."

Ramin thought, "My God, there are still people like this, with such strong personalities, in the world. They are rare, but you can still find them. People with such a high level of integrity, of ethical, moral behavior."

The technician stayed with them the whole weekend and reappeared during each of their later visits. "We spent the first weekend basically testing the machine, over and over, until the quality of the sequences achieved the level that we needed. Some of us served as test subjects ourselves until everything worked. The fact that this guy happened to be there, at the right place and the right time, really saved us."

As they left the next evening, Ramin turned to him and said, "Do you want a job in Germany?"

And the man just smiled.

Since they hadn't anticipated having to install a new sequence and run so many tests, the schedule with the family was impossible to keep. "They were extremely patient," Ramin says, but that weekend the group managed to take some of their first measurements.

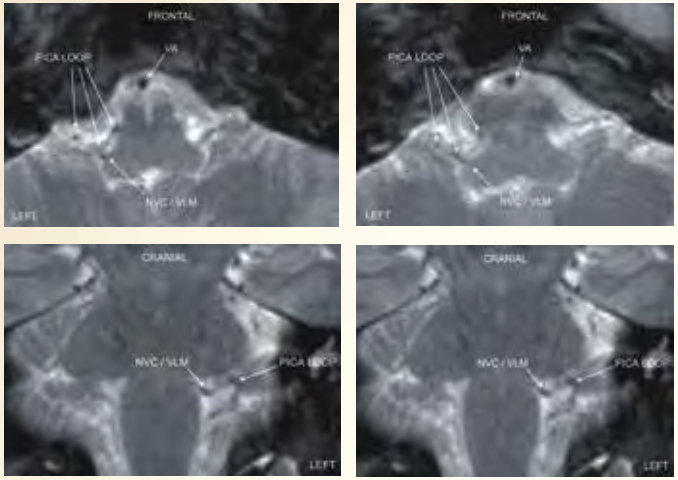
At the time MRI machines were slower; taking an image with one sequence would require twenty or thirty minutes during which the subject had to hold very still. They shouldn't move their eyes very much; even subtle movements in an MRI machine jostles the image, and then you have to start over.

"None of the family members refused, or were afraid," Ramin says. "Okan and Hakan had prepared them very well. They were brave; even the children were willing to lie in the machine and participate. I think this had to do with a very strong trust they had developed with the scientists. If you're honest with people, you can develop this type of trusting relationship."

The first procedure highlighted the blood vessels in white, and the second focused on nerves. The machine scanned each patient's brain in steps, taking an image that covers two or three millimeters in depth, then moving down to capture the next slice, and so on. There are gaps between the slices that are filled in by a second set of passes.

Over the following weekends the group usually managed to scan ten family members a day, both affected and nonaffected subjects. Ramin carried out a quick analysis in Turkey and a much more careful one several months later in Germany. He was never allowed to know which type of subject he was looking at; all he could do was render a judgment on whether the person had loops in their vessels or not.

Every time he found the loops, the image matched an affected individual, but none were to be found in the nonaffected family members. "It was extremely clear that overall, the brain vessels in affected people were strongly



These MRI images are from an affected woman from Karamat. The top images reveal transversal sections of the brainstem with the vessels adjacent to the left ventrolateral surface. The bottom images show coronal sections of the brainstem and the vessels that cause the compression. VA stands for vertebral artery; PICA stands for posterior inferior cerebral artery.

twisted and elongated; they make a lot of loops. And the vessels that they constrict are much larger than in normal, healthy people. These people have an overproportion of vessels in the brainstem, and you can see deviations in the routes they take."

The study also yielded a clearer picture of the way Bilginturan's syndrome affects the skull. "You have to understand that the condition affects the entire skeleton," Fred says. "Their whole bodies are shorter, and that works itself out in the fingers and many other bones. Ramin discovered that there's a place at the back of the skull that's shorter in people who have the syndrome; it lies pretty much right behind the part of the brainstem where he thought vessels were compressing a nerve."

In the evenings, the family invited the team to their village. Ramin was struck as strongly by the experience as the rest of the team from Germany had been. "The tea plantations are wonderful," he says. "I even brought back a tea plant and managed to keep it alive on my balcony in Erlangen for two years."

Back home, Ramin carried out his rigorous study of the brain scans, and the results confirmed the hypothesis that he had developed in light of Jannetta's work. Even the quick examination he had done in Turkey confirmed it, and so did later studies carried out on the family members living in Stuttgart. His conclusions triggered an ethical debate among the scientists that has lingered ever since.

"We were facing a big question," Okan says. "Should we offer our patients the surgery?" Wanting to get a better idea of the risks involved, he went with Hakan to discuss the case with Peter Jannetta and personally observe him perform some of the operations. After looking at the data that Ramin had collected, Jannetta said he was willing to try. If such an operation were successful, it would establish a direct causal link between the artery and hypertension.

Jannetta's skills as a surgeon impressed them during the operations. At the time, Okan says, he might have tended to offer the procedure to the family. In the meantime his opinion has changed, largely due to discussions with Fred and others who have known the family for so many years.

"Fred was very concerned that we would be offering a more or less experimental treatment which had some risks," Okan says. "Even if it's an operation with minimal complications, you would be performing it on people who don't feel very sick. It's different if your patient is suffering from intolerable pain, or has a condition that makes him willing to take a risk in hopes of a great improvement in his quality of life. There is also an East-West issue going on here: Obviously we didn't feel very comfortable as outsiders, coming in to do surgery on a family we'd gotten to know very well."

In the end Fred said "no", voicing a decision that they would all come to agree with. "Now I understand this decision," Okan says, "and I think he was right. Maybe we could have gotten rid of someone's hypertension. But if anyone had emerged with any sort of complication, everything would have changed between us and the family. We couldn't have lived with having harmed any of them. It would have destroyed the incredible amount of trust that Cafer and his relatives had placed in us for so long.

"I think before 2000, when the theme really came up, I was much more interested in changing things, and much more eager to do so. When you face a health problem, your instinct tells you to do something, if you can. Over the last ten years I have learned that doing something isn't always the best. Sometimes less is more."

The process by which he changed his mind is just one more example of growth and change that had occurred during the year, with an impact on his life that Okan couldn't have foreseen. Fred's prediction that the decision to go would change his life forever had hit right on the mark.

"Until then, I'd just been a student who wanted to be a doctor. I was still a student in Turkey, but I had the responsibilities of a doctor. It was the best possible school for me, much better than any preparation I could have received at the university.

"And during that year, the part of me which is Turkish grew. Before I left I thought about things like how much time it took other students to do their dissertation, and the fact that they can do it while getting on with their lives. I dropped out of my life. I lost one semester, and didn't see my family or my girlfriend for a year. It was a hard decision to make at the time, but now…

"Now I often watch the Turkish news, and get a feeling for the financial situation of the country and its problems; there is a lot of misery among the people. Seeing all this, living all this… When Fred Luft predicted that it would be a wonderful, very rare opportunity, he was exactly right. Personally, it changed a part of me. It completed a part of me, the Turkish part, and it was a great thing for me both as a physician and a person."

And, he says, "We really changed something for the family. Just the diagnosis and the drug study have changed something. The people now survive; they live to see the births of their grandchildren, and participate in the lives of their family. That's a great accomplishment."

16 Spontaneity

There are two ways to get Bilginturan's syndrome, something very similar, or any other genetic disease. You can inherit the condition from a parent, as the members of the family in Turkey have. Or the natural process by which chromosomes swap DNA during the creation of sperm and egg cells can produce a spontaneous case of the disease, as had happened with the Japanese boy that Sylvia discovered in the literature. That must have been the case with the woman who originally married one of Cafer's ancestors six generations ago – unless she had also inherited the syndrome from one of her parents. Only the discovery of another, more distant part of Cafer's family that branched off long ago and lives elsewhere would resolve the question.

One of the group's hopes in publishing their papers and giving talks at conferences was that more cases might turn up as scientists around the globe learned about the disease. They also kept a sharp eye out for reports related to their region of chromosome 12 and other cases of brachydactyly with the same features as the short fingers of the family. Studying the DNA of the Japanese child revealed a new border – one of the edges of the piece of the chromosome that had jumped – right in the middle of the region. It allowed the group to cut the area they had to search in half. Finding more people in whom the region had been disturbed might allow them to focus even more.

They weren't looking only for people with the syndrome. Finding someone without it, but with a disruption in the region of chromosome 12, might be equally helpful. Slightly different fragments of their DNA with different borders might have jumped around. It would allow them to draw a line that said, "If you have a problem within these borders, you get the syndrome, but if the problem lies just outside, you don't."

Within a short time they would discover several such cases, and tracking them down would send the team across the globe. Affected individuals were usually found through a series of unlikely coincidences that seemed like accidents. They weren't, really: Sometimes all you had to do to find a new case was to go about your business and keep your eyes open.

One result of publishing a paper in a prestigious journal like *Nature Genetics* is that you get invited to give talks at international conferences. If you're lucky, they are held in exotic locations and you can add on a few days to see the sights.

Right about the time Okan had left for Turkey, Sylvia Bähring made the first big public presentation of the team's findings on Bilginturan's syndrome at a meeting of the American Society of Human Genetics in San Francisco. Herbert Schuster went along. There was plenty to see in the city: You could visit the piers, shop downtown at every conceivable type of store, or ride the streetcar that ascended one of the city's hills at a perilous angle.

At the meeting Sylvia got to talk to Toshiro Nagai, the scientist who had discovered the Japanese child and had so helpfully provided DNA samples. They had corresponded, but never met. Now they had the chance to speak directly; he turned out to be just as enthusiastic in person as in his e-mails.

The society always puts on a big meeting, with parallel sessions of scientific talks from researchers all over the world and a hall full of posters. During the breaks, and a few specially reserved slots of time, researchers wandered down the rows and talked to groups who had brought a poster.

Suddenly Sylvia and Herbert found themselves in front of a poster reporting on two families that suffered from Bilginturan's syndrome. The study came from a group at the Hospital for Sick Children in Toronto, and the lead investigator, David Chitayat, was standing right there.

He had read the *Nature Genetics* paper and agreed to collaborate. One of the families was from Canada – of English ancestry – and he could send their DNA. The second was of Hispanic origin, but he had lost track of them and could no longer get samples. A few years later Chitayat found yet another family and contacted Sylvia again.

Here, too, the analysis of a new family revealed a new border within the region that slightly shortened the range that the group had to investigate. The reduction wasn't much, compared to what they had learned from Nagai's material, but every bit helped.

Okan resumed his life as a medical student, with all of its other demands, and began the long process of analyzing all the data he had collected during his year on the Black Sea coast. To write his dissertation he needed to delve deeply into what was known about hypertension for a long theoretical section; he also had to study the effects of each drug on the patients, hoping to establish what kind of treatment was likely to be the most helpful to the affected family members. The results clearly dashed Herbert's hopes of finding a single drug to address a "single" genetic problem.

That wasn't really surprising. Drug designers have always had the dream of figuring out exactly how a genetic problem – or any other kind of disease – causes problems by disrupting the activity of specific molecules in cells. If you could pinpoint those processes, you might be able to deliberately construct some sort of molecular "patch" to repair them.

But this "rational approach" is the exception: Most of the drugs used today have been used for a long time in some form, without a profound knowledge of how they work. They were usually developed on the basis of an observation that a substance has some global, desirable effect on a patient's symptoms. Systematic clinical studies were carried out to define those effects, and match them to certain patients, and then chemists came along to refine the substances to make their activity more potent.

New tools and methods have permitted scientists to zoom in on the way the substances work at the level of molecules and the even more basic level of atoms. They usually have their effects by binding onto a protein in a cell and blocking one of its activities, or maybe stimulating it to do more. A clear view of the binding process has given chemists more to work with. That would have been a logical strategy to take if Okan had been able to find a single, powerful drug. The scientists could have searched for a protein that it binds to, possibly leading them directly to a gene that had been disturbed in chromosome 12.

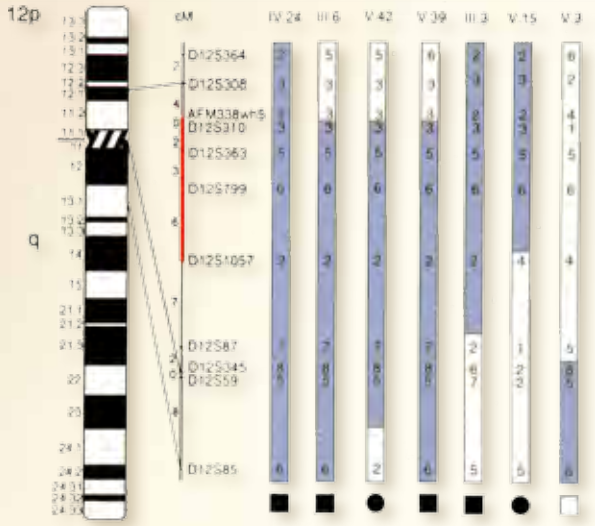
Since that hadn't happened, the researchers were going to have to keep trying to identify genes in or near the defective DNA sequences, and then working upward to understand how these molecules affected the body. It was the rational approach again; it was slow, and there was no telling how long it would take.

The alternative would be to keep working from the top down: to try to identify an organ or tissue that had somehow become defective because of the damaged DNA. The team had looked in a lot of places during the family's stay in the hospital in Berlin, but a lot more remained. Ramin Naraghi's work might be the place to start.

At the moment it looked like every affected member of the family had a compressed nerve in their brainstems, just as they all had the specific form of short fingers called brachydactyly type E. Either the loop in the artery was just another symptom that made them different from their relatives, like the fingers, or it might lead to the physiological cause of the hypertension that the team was looking for. Fred didn't think that short fingers or other features of their skeletons were likely to be responsible; a problem with a nerve seemed much more likely. Particularly when that nerve lay in an area of the brain involved in regulating blood pressure.

Healthy people have a system that monitors their blood pressure to keep it within reasonable bounds. Part of this is based on the activity of the kidneys and hormones – but those systems had pretty much been ruled out during the investigation of the six family members in Berlin. The patients' bodies produced normal amounts of hormones; the tissues that released them seemed healthy, and they seemed to have their proper effects on the kidney and other parts of the system.

But the larger nervous system also plays a crucial role in hypertension. Changes in blood pressure are detected by nerves called *baroreceptors* that extend from various places in the body toward the brainstem. The most sensitive baroreceptors are attached to two structures: a region of the *aorta* – the largest artery in the body, which the heart directly pumps blood into – and an artery that feeds the brain. This second vessel branches off from the carotid artery at the base of the neck, at about the spot where a doctor places his fingers to feel your pulse. The carotid artery runs upward close to the surface of the



Each column represents one chromosome 12 of a family member. The seventh column is from a non-affected individual. Blue bars were transmitted from the affected parent. The color change from blue to white shows a recombination. By overlapping all the information, the scientists could narrow down a common region (red) shared by everyone affected by the syndrome.

skin. Its partner, the *internal carotid artery*, runs parallel to it, deeper inside.

If you were designing a body and had to find two places to monitor the traffic of blood, these are probably the places you'd choose. A problem in the aorta would mean that something was wrong with the heart, and a change in flow through the internal carotid artery would tell you whether the brain was getting enough blood. Irregularities in either place would mean that something important – and possibly life-threatening – was going on.

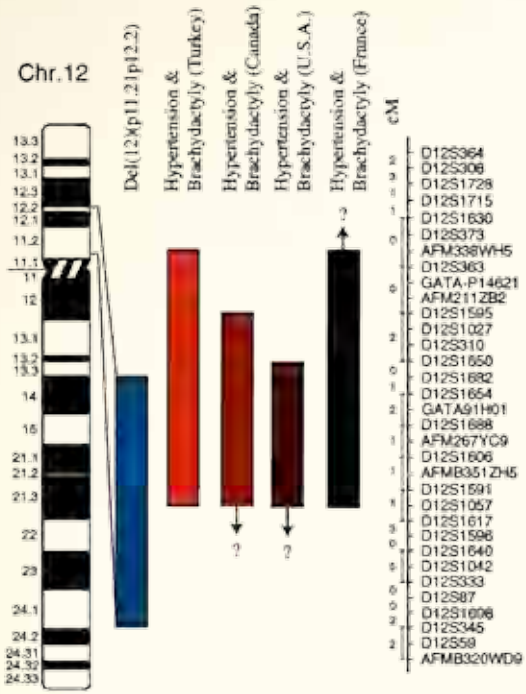
Some nerves become activated by physical changes like pressure or motion, which causes them to generate an electrochemical signal that gets transmitted to other nerves. The sensing regions of baroreceptors are connected to the walls of the arteries and get activated if they notice that the walls are stretching, which occurs when blood pressure rises. They send a signal to the brainstem, and it responds by sending new signals along the nerves belonging to the *autonomic nervous system*. This network manages aspects of our bodies that we normally don't have to think about: the heart rate, breathing, and other processes such as digestion and reflexes.

If blood pressure drops, baroreceptors become less active; this is noticed by a decision-making center in the brain. It responds with signals passed through the *sympathetic* nervous system, a subset of the autonomic system. This causes a lot of changes: the heart contracts more forcefully and beats more rapidly, and blood vessels become constricted. But when baroreceptors are activated by stretching, their signals tell the brain to slow things down. Basically, it blocks the passage of signals through the sympathetic system, and the effect is to stop taking measures that would push the pressure higher.

A problem in the baroreflex system, Fred thought, might well lead to extreme hypertension. If the brain never got a signal from the baroreceptors, or failed to switch the cardiovascular system into a quieter mode, blood pressure might keep rising and rising. He went looking for some experts to help find out.

During his year in Turkey, Okan had taken a few extra measurements using a device called a Portapress, which is attached to a patient's finger and can measure very fine changes of pulse and pressure – even those that occur from one heartbeat to the next. He used an oscilloscope to capture a glimpse of changes in pressure in the artery in the neck.

He had his patients stand up after lying prone for a while. He also made them carry out the *Valsalva maneuver*, which involves trying to force air out of your lungs although the air passage is closed. You can do this at home



Adding additional family members from the Japanese child, and affected people from Canada, the U.S., and France allowed the researchers to narrow down the locus for Bilginturan's syndrome even further.

by closing your mouth and pinching your nose; Okan used a mouthpiece that was blocked, but was attached to a monitor that could measure the amount of force they produced as they tried to push air through it. Both types of activity stretch arteries and should cause the baroreflex to adjust blood pressure.

Okan brought back the data, but didn't have much time to think about it because he was immersed in finalizing the results of the drug study and completing his dissertation. A clinical colleague looked it over but didn't find results significant enough to publish. He did notice that there were more differences between young affected and nonaffected family members; the responses of the baroreflex system tended to even out; age brought a normal drop in sensitivity.

Fred and some of the others still thought the nervous system angle needed serious attention, so once more they arranged for a group of family members to come to Berlin for tests in the clinic. This time Cafer brought over a group in their twenties. Hakan and Okan did most of the examinations with the patients, and once again arranged for some sightseeing. This time Hakan was careful about the height of the van, which had caused a problem that Cafer remembered well. And the five others who came along had, of course, heard the story.

The results of the examinations were analyzed by two clinicians who were specialists in the autonomic regulation of blood pressure: Jens Jordan and Jens Tank. They noticed that the patients' blood pressure would drop after the Valsalva maneuver. Normally it rises afterwards, which happened, but in the younger affected individuals it rose even higher than their normal level. The system shouldn't behave that way.

At that point someone remembered the data Okan had collected, and they reviewed it as well. What they found confirmed the observations from the new study. The clinicians concluded that the bodies of affected family members had a higher than normal response to stimuli of the autonomic regulation of blood pressure; this regulation was more sensitive than that of relatives without the syndrome. Since this was particularly true for younger patients, it probably wasn't a complication resulting from long-term hypertension; it was a part of their biology, their so-called baroreflex function was impaired.

The affected group had a lower baroreflex sensitivity in the first place, but it wasn't getting worse as they aged. And that's interesting, Tank reported, because the whole purpose of the baroreflex system was to keep blood pres-

sure under control; with dramatic change, it ought to step in more strongly. In people with the syndrome, the system seemed to be sluggish, or maybe even stuck in a certain position.

One other finding from the tests revealed a fine distinction between the Turkish family's hypertension and essential hypertension in the population at large. At issue was the way a person's heart rate changes in response to demands. Usually the rate increases as a person carries out strenuous physical activity. That's also what was found in people with Bilginturan's syndrome; their hearts beat at a normal rate despite their hypertension, and it beats faster when they engage in an activity that requires it.

But other people with essential hypertension usually lose their ability to make this adjustment. Their blood pressure is already high and the system doesn't try to push it higher. In other words, the affected patients' hearts were responding like those of healthy people – rather than those of most people with hypertension – when coping with activity. What wasn't normal was that the increase didn't stay within healthy bounds, considering the grave level of hypertension that their bodies faced.

Another study carried out during the visit involved trying to figure out precisely where the difference in the family's baroreflex system lay. Blood pressure regulation, as far as the autonomic nervous system was concerned, started with muscles and nerves that came into play when the body sensed cold, or became active, which would require higher blood pressure. Then if it got too high, the baroreceptors needed to sense stretching and other changes. Did the nerves themselves work? If so, they had to transmit information to the brain – could they do so? And then the system had to respond, either by using the sympathetic nervous system to do things like increase pulse and constrict vessels, or stop doing so with parasympathetic signals. Where did the difference in individuals with Bilginturan's syndrome lie?

To peel these two aspects of the system apart, Jens Jordan tried two things: he stimulated the sympathetic nervous system using stimuli such as exposure to cold and a hand grip exercise. He also used the drug phenylephrine, which generally has a stimulating effect on the system and increases blood pressure. The tests showed that the patients were more sensitive – far less phenylephrine was needed to increase their blood pressure.

Maybe their sympathetic nervous systems were overall more sensitive to stimulation. But tests showed that this was not the case. Jordan concluded that the patients must have a defect in the baroreceptors along the internal carotid artery; somehow they were misreporting the amount of pressure they sensed to the brain. He discovered that these receptors were, indeed, oversensitive.

That left one question open: perhaps the stimulation was being reported, but not responded to correctly – in other words, the brain might be stuck in a mode where the sympathetic nervous system simply raised pressure all the time, without a way to regulate it. Jordan applied a drug called trimethaphane, which imitates the action of the parasympathetic nervous system by blocking signals from the brain that normally raise blood pressure. The results showed that the family wasn't suffering from a problem in output: Even when the signals were shut down, the high blood pressure remained.

In the meantime, Hakan was moving along in his medical education: He had finished his rotations in surgery and internal medicine in Berlin, and now he was headed to the United States to do the third. While Hakan had learned a lot from the rotations in Germany, some experiences grated on his nerves. "I was constantly asked

when I would return home," he says. "I always answered, 'Return where?' Whoever asked always meant Turkey. Then I would explain that I had never lived in Turkey, and I didn't intend to return to Munich, where I was born. Even so, the nurses and patients kept calling me 'the Turkish doctor,' rather than 'Dr. Toka.'"

Okan had been called "the German doctor" in Turkey – at least until he rescued Ali from prison – but it was probably intended as a sign of respect; it wasn't a racial stereotype. Hakan was bearing the brunt of a deep-rooted problem in Germany, which had not yet changed its citizenship laws – let alone its mentality toward its huge population of Turkish immigrants and their children.

"I think it's incredibly difficult for German physicians of Turkish descent," Herbert Schuster says. "The prevailing attitude makes it incredibly difficult – even now – for them to rise to a senior position such as Chief Resident. They might become family physicians in some parts of Berlin, but even then they might have difficulty attracting 'intellectuals'. It's a shame if you're as talented as the Tokas."

But in one swift step, Hakan was about to escape any baggage of his parents' origins. His father had insisted on a rotation in Harvard, so Fred had arranged a spot in the Pediatric Nephrology department of Massachusetts General Hospital, or MGH (which carried out teaching for the Harvard Medical School). The head of the department was Julie Inglefinger, who was also a deputy editor for the *New England Journal of Medicine*. Fred knew her from committee meetings on a council devoted to research in high blood pressure.

"I traveled to Boston and stayed with a friend of Dr. Ingelfinger, a lawyer in the city. At MGH I was instantly treated with a level of respect greater than I had ever experienced in Germany. I was given office space, can you imagine?" Hakan laughs as he remembers the ten meters in the clinic in Berlin. That had been shared by his entire

group. "I was also given a lot of responsibility. Twice I was asked to present a paper on my research, and the topic I chose was Bilginturan's syndrome."

Julie Ingelfinger attended one of the talks. She approached him and said she remembered that a colleague at the Boston Medical Center (BMC) was treating a mother and son with hypertension. She wasn't sure, but they might also have shortened fingers. Perhaps he should get in touch: she gave him contact information for James Melby, an endocrinologist at the Boston Medical Center.

Hakan made the call, and he soon had an appointment with Melby. He explained his research, and Melby promised to contact the patients. When they proved willing to help, he rented a car and drove to the home of the mother that Melby had treated.

"I had handouts on our research and the equipment I needed to take blood samples, along with a consent form that I had put together based on what we had used in Turkey," Hakan says. "The family was excited that here was a Turkish/German doctor telling a story about a family living thousands of miles away with, potentially, a similar disease." After examining the woman's fingers, Hakan sketched a quick pedigree – it didn't take long because the family was so small – and had no doubt he was looking at a case of Bilginturan's disease.

Hakan had also brought along a reference book called *Smith's Recognizable Patterns of Human Malformation*, a book that used to be a "Bible" for medical geneticists. He'd dragged it along because it contained a photograph of a woman with brachydactyly type E. The image showed a woman standing and revealing her hands, followed by an X-ray image of the hands.

The woman looked at the picture for a moment and said, "That's my sister."

Hakan was stunned.

The story slowly came out: The woman in the image had been an X-ray technician at MGH long ago; her case had been published in an article by a geneticist named Lewis B. Holmes, who – another coincidence – was the geneticist at the hospital and would host Hakan during the next stage of his research career.

Hakan asked if it might be possible to obtain samples from her sister as well. The woman didn't know, the sister was living in Los Angeles, but she would call and find out. Now she would be happy to take him to visit her mother, 76 years old and living in a nursing home – after having suffered a stroke. What she could do immediately, though, was get her two brothers involved. They were unaffected and were living nearby.

While Hakan waited for a reply from Los Angeles, he started his last rotation with Lewis Holmes. "I began talking about my background, my involvement with the brachydactyly and hypertension syndrome, and told him I had found a family in the U.S. that I was recruiting."

"I know," Holmes told him. "I got a call from my former employee, who has it. I ensured her that you were a credible scientist and encouraged her to participate. I imagine you'll be hearing from her soon."

Another surprise. "His generosity was amazing," Hakan says. "Nowadays scientists are so competitive that it's equally likely somebody will block your work, especially if you are a nobody from Germany – and I was trying to recruit a former employee that he knew personally!"

Holmes was particularly interested because he had published his report on the family at almost exactly the time that Nihat Bilginturan's original paper appeared. But he had focused exclusively on the fingers and completely missed the fact that the family had a hypertension phenotype that accompanied it.

The sister from Los Angeles gave him a positive response right before Christmas. Hakan needed to fly to Los Angeles, but he couldn't afford the ticket. He had been in touch with Fred Luft the whole time, so he contacted his mentor and asked if he could get some money for expenses. Fred couldn't manage it, so Hakan called his parents. Yes, he could charge the flight to their credit card.

He arrived in Los Angeles on Christmas Day and the only vehicle available for rent was a huge van, larger than anything he'd ever driven before, even larger than the one he'd failed to drive into the parking garage in Berlin. Somehow he managed to maneuver the vehicle through

Los Angeles without an accident and met the patient at her home in Hollywood Hills. He left with a Christmas present: sample tubes containing her blood and that of one more family member who had agreed to participate.

From Boston, he shipped off the frozen samples to Fred and Sylvia. Combined with the information they obtained from the Canadian family, the group could once again significantly narrow the genetic locus on chromosome 12.

On the last days of his rotation, Hakan had lunch with Lewis Holmes. "He quoted Louis Pasteur to me," Hakan says. "'Chance favors the prepared mind.' I couldn't agree with him more."

At a dinner table in Ankara, the group collectively told me the story of their next trip, which arose from another chain of odd coincidences. We had come to talk to Nihat Bilginturan, and the evening before the meeting, we sat around the hotel table drinking wine. Once again the story arose from a serendipitous discovery of Hakan's, this time in the library of Massachusetts General Hospital.

"By this time I was an expert on brachydactyly type E," he says. "I found an article mentioning a case that had been written in 1980 for the *South African Journal of Medicine*. The abstract looked interesting, and I flipped to the X-rays of the hands that had been printed in the article."

Not only did the family have "dominantly inherited short stature, short broad hands and feet, normal facial appearance and normal intelligence," the characteristics that Fred's lab was looking for, but the X-rays revealed the cone-shaped epiphyses at the joints between the fingers that was a particular feature of the Turkish family and the other subjects. To no one's great surprise, there was no mention of hypertension in the report.

Again Fred Luft received a call from Hakan. He must have been getting used to this.

"Where are they this time?" Fred said.

"South Africa. The author is someone named Jennifer Cartwright."

"All right," Fred sighed. "I'll get in touch with her."

Cartwright agreed to a collaboration and promised to get in touch with the family. They heard back from her soon. Yes, they could come.

By the time they were ready, Hakan had returned from the US, so he boarded a plane with Fred, Sylvia, and Herbert for a twelve-hour flight. It was strange, Fred says, because it flew directly south, with no time change. When you got out of a plane after that long, you expected jet lag.

It turned out to be a wonderful trip for all of them, but Fred says, "At first it looked like it was going to be a bust." They were greeted by Cartwright, "a lovely lady, quite 'English'," Hakan says, who showed them around the pediatric hospital.

A day or two later she introduced them to the family. They were white and very poor and served their visitors food in their small back yard. Everyone agreed that the hands looked right for Bilginturan's syndrome, and they took blood samples.

The blood pressure of the subjects had to be measured, of course, so Fred and Herbert hooked them up to the gauges. Their first subject was an affected young man.

Then came the bad news, depending on your perspective: His blood pressure was perfectly normal. "Another one had hypertension," Fred says, "but it was an older person where you might think that it's a normal effect due to age."

It meant the family didn't have Bilginturan's syndrome, which was a shock; with a single measurement, the whole

trip seemed to have become a waste of time. The scientists returned to their hotel, which looked like a country mansion, where all the personnel were black. "It made you feel like a colonialist," Hakan says. "We'd seen poverty in parts of Turkey, and now we saw it in South Africa; the difference was that here, the rich lived a stone's throw away, just behind all the high walls with barbed wire on top. They lived in enclaves."

They settled in to drink South African red wine and briefly discussed the family. There seemed to be nothing left to do but enjoy themselves the last few days. They took a trip to a wildlife park, which boosted their spirits a bit. Hakan did the driving – South Africa uses the British system where you drive on the left, and he was the only one willing to risk the experiment of driving on the wrong side of the road.

"I was driving down the street and, of course, I kept drifting over to the right," Hakan says. "Herbert was acting as co-pilot and trying to read the street signs. Which, you should know, had red lettering printed on a green background."

"You know that Herbert is severely color-blind," Fred remarked.

"So we got totally lost," Hakan laughs. "I have no idea how we got back to the hotel."

A day or two before their departure, Fred was asked to give an impromptu talk on the group's research. "Well, okay, I told them, but I hadn't brought my Mac; I didn't have anything along."

He put something together quickly and gave the presentation to a group from the pediatric hospital. "Somehow I managed to get through without a crash landing," he says. "And I was just about done when somebody in the audience stood up and said, 'Oh, I have one of those!'"

It turned out that a physician in attendance did indeed have "one of those," and the group managed to see the patient before the end of the trip. It was only one person, unrelated to the family they had come to investigate. But she did turn out to have Bilginturan's syndrome, with all the hallmarks, from the fingers, to the height, to an impressive case of hypertension.

"The remarkable thing about this story," Fred says, "is that we went to South Africa for a week with one expressed purpose. That didn't work out, but instead we found this separate individual whom we'd never have discovered otherwise. If you think of the odds of that happening…"

Chance favors the prepared mind.

In the late 1990s, the original team that had started the project on Bilginturan's syndrome at the Max Delbrück Center began to dissolve, in the natural way that scientific groups do. The Toka brothers would move on to continue their medical careers. Hakan would move to the United States, perhaps for good; Okan would receive a position at the university hospital in Erlangen. Thomas Wienker, who had never enjoyed the type of independence that came with having a group of his own, was offered a professorship in Bonn. It was a great opportunity that came at just the right time; he still felt discouraged about the authorship issue that had arisen from the project's first paper. Herbert Schuster would eventually leave to start his own company and establish a private practice in Berlin. An important core would remain: Fred Luft, of course, and Sylvia Bähring, and Atakan Aydin. And the group would acquire new members and partners that would bring the project further.

Philipp Maass

17 The discovery of slowness

In 1998, Fred and Herbert met a young student named Philipp Maass at a medical meeting in Frankfurt. Philipp had just finished his high school diploma and had a few months before he had to report for his period of compulsory military service. He had already decided against following too closely in the footsteps of his father, a cardiologist in Kassel; Philipp wanted to become a molecular biologist. That was fine with his father, who recommended that he get some experience in a lab before going off to work in some area of the military he can't talk about – "I'd have to kill you," he might say. (Well, he'd never say that, he's too nice, but I can read between the lines.)

His father took him along to the conference with the express purpose of introducing him to Herbert Schuster. Herbert was an old acquaintance who had enhanced his medical career with research in genetics and molecular biology. Maybe he could take Philipp on for a couple of months and give him idea of what he would be getting into. Philipp met Fred Luft and Herbert at the meeting, who said, "Sure, come on over."

Later Philipp and Fred would find a point of common history: Bad Wildungen was close to the area where Fred had been relocated as a child, near the dams that the Allies had bombed during the Second World War. Fred had relatives of his own in the area and

visited from time to time. He and Philipp knew some of the same bike paths.

In the fall Philipp borrowed one of his parents' cars and headed East. "The quality of the highways was still really bad," he says. "At one point I saw signs for Warsaw and thought I'd gotten hopelessly lost in the East German forests. But somehow I finally made it to Berlin-Buch, and they put me up in the MDC campus guesthouse."

He spent several weeks in the lab working alongside Atakan and other members of Herbert's group. Sylvia had taken time off to have a child, and Heike Baron was in charge of the day-to-day operations.

While on the campus, Philipp had an unusual encounter with Detlev Ganten – unusual if you didn't know about Detlev's habit of roaming the campus buildings at night, or his tendency to appear at the precise moment something interesting was happening.

"There were a lot of Asian students living in the guest house," Philipp says. "The Indian and Chinese students would often cook dinner late at night, and one evening – it must have been around 10.30 pm – they burned something so badly in the microwave that they set off the fire alarm. It wasn't the first time it had happened, so we knew what to do. I ran up to the security office to tell them it was a false alarm; otherwise the fire department would come and it would cost a couple of thousand of marks. But I was too late; they were already on their way."

When he got back five or ten minutes later, Detlev Ganten was standing in his kitchen. Philipp had never met him, but recognized him from photographs in MDC reports. "He asked me who I was and what I was doing at the MDC, and I told him I was working in Professor Luft's lab." They talked about research for a little while, and a few minutes later Detlev was on his way again.

Over ten years later Philipp, now a full-fledged member of Fred's lab, was waiting to pick up a Chinese professor at Tegel airport. He saw Detlev Ganten and his wife at the next gate, waiting to board a flight to Switzerland. The (former) director immediately recognized him and remembered that he had been in Fred's lab. "He asked me what I was doing and I told him that – once again – I was in the same lab at the MDC, this time finishing my PhD. It was incredible that he could remember one student he had met one time, in the middle of the night, in a guest house kitchen during a fire alarm."

In the lab he started with the basics: DNA extraction, PCR, and pipetting, and other techniques and sat in on group meetings involving Fred and Herbert that he found fascinating. When the stay was over, Herbert gave him a letter of reference and said, "Call me if you ever want to come back." The team had failed to scare him away from molecular biology. By the time he set off for his military service, he was firmly hooked.

With the original linkage study and information from the new patients in Japan, the US, and South Africa, the team had carved the crucial area of chromosome 12 down and down as far as they could. It was time to take a look inside the region, but what were they searching for?

Most things in the body of a person with Bilginturan's syndrome work perfectly well; otherwise an affected person would never survive 30 or 40 years. Ultimately, the difference in their bodies likely boils down to this: certain cells, at specific times, fail to produce a certain molecule important in shaping a "standard" human body.

A protein was the most likely candidate; proteins that are missing or somehow deformed lie at the heart of many severe genetic diseases. The alteration of a single nucleotide in the gene sequence of a protein can render it unable to do its job. Even though studies of genes in the region hadn't revealed any sequences that could be

linked to the disease, the problem might not lie in the gene itself – a variation in its "control regions" could have the same effect.

But to show that such a variation is responsible for Bilginturan's syndrome or anything else, you had to know what gene you were dealing with. And before you could do that, you had to know that the gene existed in the first place. In the year 2000 – and usually even today – this situation has caused a chicken-and-egg problem that is almost impossible to resolve.

Sometimes there's a shortcut. Scientists had already identified genes that led to the development of short fingers, or to the regulation of hypertension – a lot of different molecules were likely to be involved in each process. But information on these processes was very limited, especially in the case of blood pressure. And it didn't help that nearly everything that was known came from laboratory animals such as mice and rats, whose biology might (or might not) reflect the functions of genes in humans.

Another chicken, another egg. Or, as Fred Luft puts it, "More tears in beers."

In the late 1990s, the group had no specific idea of what they ought to be looking for, so they started sequencing the region to obtain the letter-by-letter spelling of its DNA. Technically, this could be done, but it was extremely difficult and would take years. The lab discussed the situation – should they start their own "library" of the family's DNA? "It would have meant taking a patient's DNA, sequencing like mad, and then screening millions of sequences to find a few hundred. Those would have had to be 'assembled' into a single string – a complete 'map' of that area of the genome."

And the main problem was: Whose DNA should you use? Everyone's genome contained lots of variation compared to each other person's; in fact, each affected individual held a healthy version of chromosome 12 alongside the sequence that had been affected. At the time, scientists didn't really have an idea of how dramatically different two genomes could be.

And that's still the case, despite a revolution in biology that has been happening since the group began sequencing. Scientists were about to complete a "working draft" of the entire human genome. It was a huge step, of immense importance to the whole of biological research. But for single groups, such as Fred's team, it wouldn't mean very much for a long time. Instead, they kept scanning the region for genes, hoping to find one that would show signs of a significant variation.

Building a map of the entire human genome was a wonderful idea, a fairly simple one, and it clearly held great potential over the long term. From the point of view of many scientists, those benefits were "sold" to the public a bit too optimistically, raising expectations of short-term medical benefits.

As Philipp finished his military service and started an undergraduate degree at the Eberhard-Karls-University of Tübingen in southern Germany, Bill Clinton and Tony Blair held a press conference to announce the completion of the Human Genome Project. Well, sort of. The plan had been to obtain a complete, letter-by-letter list of all the nucleotides in the 46 human chromosomes. In fact, ten years on, the project still isn't finished. There are still gaps in the information, and it turns out that there isn't one genome – everyone's is unique. We still can't estimate the true extent of "normal" variation.

But enough had been done in 2000 that scientists could present a "working draft" of the genome. If you were a subscriber to the journal *Nature*, you received a free copy of it on a CD-ROM. You would have needed to throw it out and replace it in 2003, when a more complete version of the genome became available, and then many more times as new versions have appeared. In fact, the genome

sequence is being updated every day, so you might as well turn to the on-line version. That's what scientists do; none of them used the CD.

Reaching the 2000 landmark had required the constant operation of huge "farms" of DNA sequencing machines, like the one Atakan Aydin and the other members of Herbert's group had been using, but for a different purpose. The effort required thousands of these instruments, in laboratories all over the world, working night and day. Nobody quite knew what would be done with all the machines after the project was finished. You could use them for paternity testing, for example, but hopefully there wouldn't be that much of a demand. In fact they have been put to many uses, including genetic screening, finishing the genomes of other organisms, trying to discover mutations that cause cancer – and, of course, paternity testing.

Already the sequence was serving as a sort of skeleton that people could hang information onto, a reference book. If you submitted a paper that provided new insights into a gene's sequence or functions, journals now required you to enter this information into the database. It became a general reference that scientists all over the world could access. Anytime someone discovered a piece of information about the sequence or contents of the group's region of chromosome 12, it should appear in annotations of the human genome.

Yet a standard genome doesn't really exist. So narrowing in further on a particular sequence, such as a gene, means filtering through a vast amount of noise to focus on one thing – maybe several things – that make a crucial difference. This might seem surprising given daily headlines that announce the discovery of new links between genes and disease. But most of these projects have started the other way around: A researcher already working on a specific gene discovers that it causes symptoms like a human disease, usually in a mouse or another experimental animal, and then discovers a similar defect in the tissues of human patients.

Starting with humans and working in the other direction requires a particular type of determination. Sylvia Bähring puts it another way. "I'm curious," she says, "I want to *know*. And although everything about the way science usually works can discourage that – the insistence on getting results and publishing – it's what keeps you going."

The collaboration that Detlev Ganten established with China in the early days of the MDC had already made itself felt years ago with the sudden appearance of Mr. Zhou. Now the cooperation agreement had another effect through the arrival of another Chinese scientist at the MDC. This time there was a good match, because she was working on the genetics of hypertension.

Maolian Gong arrived in Berlin to join the group of Norbert Hübner as a PhD student. She brought along a project based on a large population living in an isolated area of China, called the Shijingshan district. They descended from a small original group that had settled in the region, and centuries of interbreeding had clustered certain forms of gene variants at a higher rate than in the population at large. As a result, some families suffered a form of essential hypertension in much higher numbers than the general population of China.

Unlike in Bilginturan's syndrome, the group's hypertension did not follow a Mendelian pattern; more than one region of DNA was responsible. Theoretically, you could still attempt a linkage study, because people with the disease would still share the genetic elements that were responsible, but it would be more difficult. The "signal" from a particular region of the genome would be weaker, because it didn't bear responsibility for the condition alone, but you still might be able to find it. The

work would require more sophisticated statistical programs than the ones Thomas Wienker had used and developed in studying the Turkish family.

Maolian and Norbert selected 94 individuals with essential hypertension and began the whole long process that Fred's lab had been through: developing markers based on finding microsatellites, running gels, and putting the results through a statistical analysis. They found regions that looked interesting, but none of them reached the magic "LOD score" number of 3. They found additional sites for the placement of markers, in hopes of finding new recombination sites. The LOD scores climbed up and up, from 2.82 to 2.85, but still didn't reach 3.

Now the team added 174 more people to the study, this time taking close relatives – parents and children – from 32 families. When they combined this new data with that of the individuals who had already been studied, one region that jumped to a score of 3.44.

The region overlapped nearly perfectly with the locus found by Fred's group on chromosome 12. The Chinese subjects didn't have short fingers, which was a bit puzzling. But a completely independent project had homed in on the identical region; it was an important confirmation that the locus found by Fred's group played an important role in hypertension.

The human genome sequence held some major surprises for biologists. First, there were far fewer genes than most scientists expected to find. A scientist responsible for the public genome database in Great Britain organized an unofficial betting pool in which scientists guessed the number to be found. Few guesses fell below 30,000; a few brave souls estimated numbers upwards of 300,000.

As it turns out, the number of true genes probably lies between 20,000 and 25,000, and is likely toward the low end of that range. That was astounding, because the tiny fruit fly, made famous by Thomas Morgan, had about 14,000 genes. It seemed incredible that evolution could produce a larger, much more complex body by adding so few genes. And the DNA sequence of wheat has 42 chromosomes and five times as many letters as the human genome. Chromosome 3B alone is estimated to contain about 6,000 genes.

The human sequence showed that most genes were broken into tiny bits, with the coding sections used to make proteins (called *exons*) scattered widely apart and interrupted by long sequences called *introns* that didn't seem to do anything. Nearly every gene had them – the average human gene contains more than eight. Introns are transcribed into RNA along with the coding regions but are then removed, leaving only the exons and some sequences at the beginning and end. The process of removal, called *alternative splicing*, means that proteins of different lengths and forms can be produced from the same gene.

Another surprise was that the genome was littered with millions upon millions of repetitions of small groups of letters – like the microsatellites; they didn't seem to have any function, either. These regions were highly variable from individual to individual – which made DNA fingerprinting possible. They had undergone lots of duplications and translocations. If these changes disturbed the structure of a gene, the cell might produce an improperly formed version of the molecule, or none at all.

Initially all of this information was simply considered superfluous "junk", like excess baggage that had been acquired during evolution and hadn't yet been thrown out. But with the development of new, very sensitive methods to capture cellular RNAs, scientists discovered that a vast amount of the non-coding information in the genome

was being used to produce RNAs. It isn't junk at all; it has important functions. So the problem in Bilginturan's syndrome might center around an RNA, rather than directly affecting a gene, and that required thinking about the disease in a different way.

All the way along, Sylvia and her colleagues had been facing the problem of sequencing the region of DNA in chromosome 12 – at least, somebody's region. At first it might not make much difference whose. Since the team's original assumption was that the problem affected a gene, the first goal was to discover any that might be located in the region. Once those were found, you could compare any variations you found, trying to match them to the pattern of inheritance in the syndrome.

The first step in sequencing was to obtain a collection of DNA from chromosome 12 in the lab. Originally this was done by cutting a human genome into large fragments using DNA-cutting enzymes; the pieces were glued into circular structures called *plasmids*, which were then inserted into yeast cells or bacteria. These structures, called *yeast* or *bacterial artificial chromosomes* (YACs or BACs), were copied every time the cells reproduced, and then you could harvest plenty of DNA from them.

At first you didn't know what part of the genome the YACs contained; to find that out, you had to find a bit of sequence that matched a unique string that had already been found in unique region of a chromosome. The well-known microsatellite markers were used to say, "This fragment belongs to a region of chromosome 12 we are familiar with."

Assembling this information was a major task during the Human Genome Project, and experts on each chromosome met in international workshops. Sylvia attended two or three meetings on chromosome 12. "They were real working sessions," she says. "People came and pooled everything they knew and put it onto the map."

This was done for the entire genome and eventually gave researchers a huge "library" of plasmids which, theoretically, covered the entire genome. But without a reference – a map showing where everything ought to go – that was hard to do, and mistakes were made. Sometimes during the building of a plasmid, fragments of DNA from other chromosomes were brought in by mistake. This led to mistakes such as the creation of false sequences that never really occurred in the genome, and detecting such mistakes was a huge challenge.

Developing good libraries was a long, tiresome process. But each step forward meant that the team could order some of the YACs or BACs they needed from other groups working on the genome, instead of making them all on their own. They could compare sequences from the library to material from their patients, and could start sequencing from the ends of their region and working toward the middle.

Sequencing machines could only read a couple of hundred bases at a time. The scientists started at one end using a sequence that they knew, attached "primers" that would start a copying reaction in the PCR machine, and ended up with DNA just from this region. Now they had to do the actual sequencing, which once again used the lengths of fragments, now to determine what letter occupied each position in the DNA.

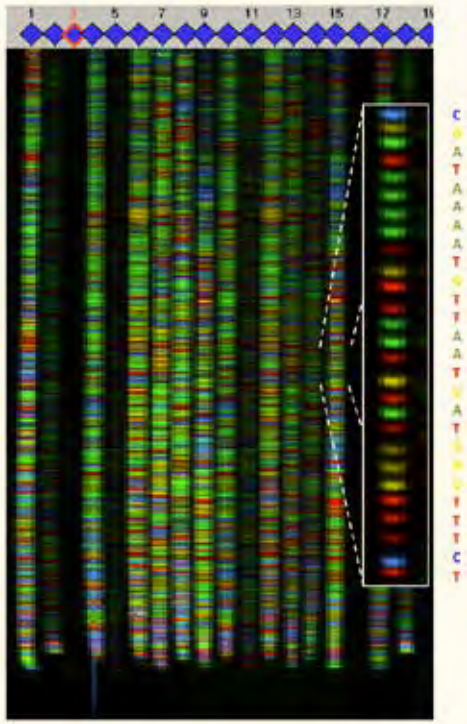
The method they used was originally developed by Frederick Sanger, a researcher in the United Kingdom, who won a second Nobel prize for the invention. (His first award came from work on determining the sequences of proteins.) Sanger's method was based on the process by which cells copy their DNA. Scientists put single strands of DNA into a solution that contained free-floating nucleotides and the replicase molecule that assembled them into a second strand. Sanger and his colleagues had

built special versions of the four nucleotides called *dideoxynucleotides*, or ddNTPs, which were lacking a part of their chemical structure. The replicase couldn't tell whether it was adding a normal nucleotide or a ddNTP to the strand. When it picked the first, the replicase inserted it and went looking for the next nucleotide. When it picked a ddNTP, the reaction stopped right there.

The reactions were carried out in four separate solutions, each containing a ddNTP version of one of the nucleotides A, C, T, or G. The same fragment was dropped into each solution, starting at the same sequence and running a few hundred nucleotides long. The replicase integrated the ddNTPs at random places, leaving fragments of different lengths. They were loaded into the gel of the sequencer, and it measured their lengths as they came out the other end. The "A" column would report fragments that were 10 nucleotides long, then 12, then 20, and so on. This means that positions 10, 12, and 20 in the sequence were the letter "A", the reaction was terminated with ddATP. The "C" column might show fragments of 11, 13, and 14 nucleotides in length, and this meant that those positions were occupied by the letter "C".

The original Sanger method was then developed further. Each "terminator" was labeled with a different fluorescent dye for each nucleotide. Earlier, four "lanes" of the gel had been required to obtain a readout of the four bases of the sequence; now you could do the whole thing in a single lane. The labeled DNA fragments were separated by size during electrophoresis and the bases were determined by the different fluorescent dyes.

Each new sequence brought the group a few hundred bases farther into their region of chromosome 12. At the ending point they had to build the next primers to take them just a bit farther, over and over again. It was an immense task that would take years, with no guarantee of success. The sequences might vary so widely between affected individuals that you might not be able to extract a common pattern – which you would then have to compare to all the nonaffected people.



The new Sanger method permitted seeing all four bases in a single "lane", or column. Previously it took four lanes, for each nucleotide and ddNTP, to read the nucleotides in a sequence.

"At first we sequenced only the BAC clones," Sylvia says. "If we found something that looked like a gene, then we picked about three affected and three non-affected individuals from all the families we had. Atakan and Eireen Bartels-Klein did most of the sequencing."

Since most regions of the genome hold small, widely scattered fragments of genes, it was going to take the group a long time to move through the locus.

Sylvia didn't even want to think about it.

Sylvia checked every new sequence that the group discovered with knowledge that was steadily pouring into the databases from other groups. One day there was a hit: a sequence was highly similar to a protein found in rats, called *SUR2*. Humans were likely to have a version of this molecule as well – most genes, especially in closely related species like rats, are "conserved" across evolution. Their sequences aren't exactly the same, because they have changed over hundreds of millions of years of evolution, but they are close enough that computer programs can detect the similarity.

Scientists did know, however, that humans had a gene called SUR1, which stands for *sulfonylurea receptor 1,* which was closely related to Sur2. It had been extensively studied by a team in Houston, Texas. Gene duplications over the course of evolution have often given species several copies of a molecule that started out as a single gene; each copy undergoes different mutations that may lend different functions to the protein that it encodes. Or they may render it dysfunctional.

"They worked out the structure of the mRNA produced by the gene," Sylvia says. "Then together we figured out the structure of introns and exons in the gene, and that helped as we started to work on SUR2. It had a very complex structure, with 39 exons."

The molecule was part of a *potassium channel* that sits in the membrane of cells and allows the passage of positively-charged ions through the membrane. This has many effects: for example, it helps nerve cells pass along electrochemical charges, and sometimes helps cells release other molecules. SUR1 was a target of drugs used in the treatment of diabetes. The drugs docked onto SUR1 to promote the release of insulin and help ease the symptoms of *type 2 diabetes*.

This disease is common in people who have gained weight and do not get enough exercise as they get older; their bodies become insensitive to the hormone insulin and are less able to convert sugars in foods into energy. A common symptom is a rise in blood pressure.

The discovery gave the group their second real candidate as a gene that might be responsible for Bilginturan's syndrome. The first had been PTHLH, discovered by the time the very first linkage study was published in *Nature Genetics*. That one had been discarded because the scientists couldn't find a mutation common to all the affected individuals and yet different from all of those not affected.

Now PCR was used to make copies of SUR2 from every family member and then sequence it. Once again, the team failed to find a mutation that could be linked to the disease.

Later they would have the same experience with a gene called *Kir6.1*, another subunit of the potassium channel that contributes to the activity of SUR2. Then *PDE3A*, which plays a role in the functions of muscles in the heart and blood vessels. It was another promising candidate because defects in these tissues might be expected to play a role in high blood pressure.

If the group couldn't find a gene in the target area, maybe they needed to expand their investigation to molecules lying nearby. Such genes might still be affected because a control sequence lying inside the region might have experienced a mutation or some other kind of change. That might block the use of the gene at a crucial moment, or its activity might *need* to be blocked – and cells could no longer shut it down.

One sequence that was still in the linkage region was the gene *L-SOX5*, whose functions were unknown. One day Sylvia received an e-mail from Véronique Lefebvre, a

French scientist working in Cincinnati, Ohio. In the mail she stated that she had discovered one of the functions of the molecule. L-SOX5 encoded a protein called a *transcription factor*, which activates other genes. In mice, one of its targets was a molecule called *collagen type II*.

"That was interesting," Fred says, "because L-SOX5 is produced in the tips of the toes, the long bones, and the vertebrae of developing mice. Collagen type II is a tough, gibrious protein that is the main component of bone and cartilage. This made L-SOX5 a great candidate gene in terms of explaining the skeletal anomalies in patients. So we thought we'd better sequence the entire human gene."

That took another year. L-SOX5 turned out to be a monster, over 500,000 base pairs long. A huge number of variations had to be checked; every time Sylvia found a change in a single letter of the sequence, she compared it to the pattern of inheritance. And once more, there was no consistent pattern.

The investigation of each molecule required over a year. A lot of time was passing by; the institute and other scientists were getting skeptical about continuing to fund the project, and the group still didn't have any idea what caused Bilginturan's syndrome.

18 Upside down and sideways

By the end, after having sequenced every known gene in the linkage region, Fred and Sylvia were no longer sure that the problem lay within a gene itself. But new methods were becoming available to look at other kinds of changes in DNA, for example, some sort of rearrangement in the linkage region. During the recombination events that occur as sperm and egg cells form, a fragment might be plugged into a chromosome backwards. If such an inversion had happened, you wouldn't be able to tell by sequencing: the machine didn't know whether it was reading a bit of the genetic code forwards or backwards.

One of the new technologies that could this hypothesis, however, was called *fluorescent in situ hybridization*, or FISH. (Sometimes acronyms work out.) The idea was to attach fluorescent probes to regions of DNA and look at chromosomes under the microscope. To look at a small region you had to do it during *interphase* – the stage of the cell cycle when its DNA spreads through the nucleus in loose strands.

It was a bit like setting up a row of flags of different colors on a geological fault line and then waiting for an earthquake. Afterwards the positions and order of the flags could tell you whether something had moved, and how.

Just before Christmas, in 2001, Sylvia saw an article reporting that FISH had been used to demonstrate an inversion on a human chromosome. She went to visit a colleague named Anita Rauch, who could do the experiment but was skeptical. First the group had to find sites within the Turkish family's DNA sequence where the fluorescent "flags" could be attached, and then she would see.

By 2002 the group had sequenced enough of the linkage region on chromosome 12 to find five places to attach such flags. Using libraries of bacterial artificial chromosomes (the BACs that the grouped had been developing during their sequencing efforts), Sylvia picked out five positions close to the PDE3A, SUR2, and SOX5 genes that would be useful.

The next step was to "fix" the DNA architecture in interphase cells of *fibroblasts* and *lymphoblasts* (LCLs) that had been obtained from the blood samples of the family members during the earlier visits.

"It was hard to capture lymphoblasts – they are a sort of stem cell that usually specializes into lymphocytes," Sylvia says. "You 'immortalized' the cells using viruses, which permitted us to grow them and keep them alive in the laboratory." That task, Sylvia says, has fallen to Astrid Mühl, who has taken care of the cell lines of every patient over the years.

The experiments took until the end of 2002. Sylvia attached red, green, and yellow fluorescent markers to specific locations in the DNA from the BACs and inspected their arrangement in the cells of the Turkish family.

The results were undeniably clear: the DNA of every affected person revealed that a sequence inside the region had been inverted. And none of the nonaffected family members had it; the probes in their sequences had the normal order: 1, 2, 3.

It was already a wonderful finding; finally, something had worked. "But the real test was to look at the same sequences in the Canadian and American families, as well as the child from South Africa," Sylvia says.

"In each of the families, FISH showed us that rearrangements had occurred," Sylvia says. "Interestingly, each family and the child had shuffled things around a bit differently. But the same region had undergone some type of disruption in every patient."

While there weren't any mutations in genes such as Kur6.1, SUR2, or PDE3A within the linkage region, and L-SOX5 lay just outside, the inversion might have disconnected the genes from their control regions. This meant that it was time to bring some real molecular biology into the project.

Cells in tissues such as blood vessels might still have the genes but be incapable of using them properly. There was a way to test this by measuring the amounts of messenger RNAs produced from the genes in affected and nonaffected family members. A disruption in gene control might give one group an insufficiency in a particular molecule, or make it more abundant than it ought to be.

The measurements would require obtaining samples of tissue from the patients that contained blood vessels. So once again, members of the Turkish family were brought to Berlin, accompanied – as always – by Cafer. This time ten individuals came along: six who were affected and four that weren't.

In planning their arrival, Fred had met with Jens Jordan and other colleagues to think about getting the most from the visit. They brainstormed on every method they could think of that might shed some light on the physiology of hypertension. More meetings with Sylvia and the gang focused on the molecular biology.

"We could obtain a sample of blood vessel through a relative simple procedure to remove tissue from a patient's buttock," Fred says. "Still, it was surgery – and elective surgery, not directly aimed at improving the person's health. You never want to do that unless the whole

procedure has been ironed out perfectly in advance."

To do that they needed a guinea pig, and Fred volunteered. "So don't say I haven't ever put my ass on the line for this study," he says.

Hospitals like the Volhard Clinic routinely carry out surgery and other procedures if the aim is to treat a patient, and insurance companies pay for it. But doing the same things in the name of research is a different matter. Over the years Fred had helped develop a unit within the Franz-Volhard Clinic called the Clinical Research Center, or CRC, to take on this type of task. It was headed by Jens Jordan. HELIOS, the corporation that now owned the Franz-Volhard Clinic, sponsored the visit and didn't charge the team for the hospital stay or any of the tests that were performed.

The small operation left the patients sore for a few days, but otherwise none the worse for the wear. (Except for having to give up smoking during the stay in the hospital.) They underwent a few more tests involving the way their vessels and blood responded to drugs.

Careful dissections of the biopsies yielded one payoff regarding the affected patients' blood vessels: they showed signs of *hyperplasia*. In other words, the smooth muscle that surrounded their arteries had more cells, making the muscle bulkier. This hinted that the PDE3A gene might be involved, because smooth muscle produces the protein.

If affected individuals had differences in the activity of their PDE3A gene, the vessels might not be as sensitive to contractions and dilations as in people with a gene that was controlled in the normal way. This could be tested, Jens suggested, by inserting a cannula in a forearm artery to take measurements of blood pressure and the behavior of drugs – such as a PDE3A inhibitor – directly within a vessel. The researchers inserted the thin channels, applied a cuff to isolate the arm from the hands, and used drugs that typically affected the contraction and expansion of the vessels.

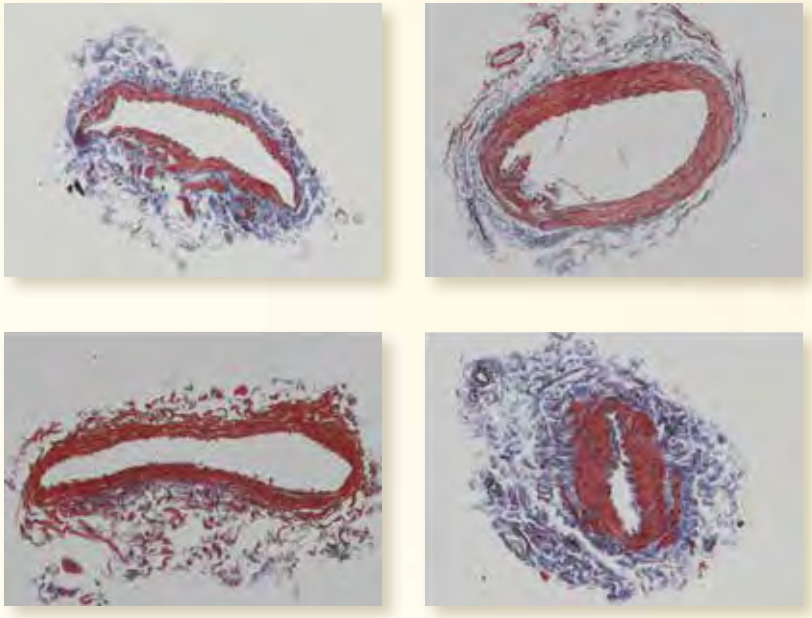
Other substances were used to open and close cell membrane channels such as SUR2 and Kir6.1 to test for changes in the rate of blood flow. Unfortunately – in terms of an ultimate explanation for the hypertension – no significant differences between the groups of subjects could be found.

Another experiment using the *patch-clamp method* could test the activity of the ion channels. This involves attaching a microscopic glass pipette to the membrane of a cell, sealing off a small "patch" of the membrane that would hold a few ion channels, and filling the pipette with a charged solution. An electrode is inserted into the pipette. It measures changes in current that occur when the charge of the solution is changed. If the ion channels in the cell membrane work properly, the cell should adjust to the changes in the solution in predictable ways, and its response can be measured by the electrode.

The experiment revealed that the ion channels of affected and nonaffected people seemed to respond in the same ways. Another strikeout.

Studies of the material obtained in the biopsies did show that older affected individuals produced higher-than-normal amounts of PDE3A than their nonaffected counterparts; in young people there was, once again, no significant difference. Since blood pressure rises with age, this might somehow contribute to the problem. On the other hand, it might simply be a by-product of living with the hypertension for long periods of time. The differences weren't large enough to get excited about.

Sylvia and Fred wrote up a paper explaining the inversion of elements within the linkage region and got it published in the journal *Hypertension*. They added all of the failed experiments as well. Often you omit anything that doesn't work – even though leaving a record of the fail-



The arteries of affected individuals are surrounded by more smooth muscle cells, making them bulkier than those of nonaffected people.

ures might actually be just as important. Negative results could save the next person to come along from wasting years of his lab's time, only to get more negative results and leave them out of his paper, and on and on…

But good luck getting that kind of thing published.

All of this work was happening against a backdrop of significant changes at the Max Delbrück Center. Fred found himself increasingly distracted by politics and long-term planning as the institute expanded, went through changes of directors, and tried to develop new infrastructures to try to bring clinical and experimental research together.

"The Charité Medical Faculty's interest in the clinical departments in Berlin-Buch was waning," Fred says. "It was completely unclear how the relationship between the Max-Delbrück Center and the Charité was to proceed in terms of translational research, for example in our project."

A major grant had to be written and Fred took the lead in writing the section on clinical research. He envisioned a "Clinical Research Center," or CRC, that would be operated independently of patient care. "In that way, funding sources and payments could be kept separate and transparent," Fred says. "Detlev Ganten saw to it that more basic research was included in the proposal. The grant application for the Experimental and Clinical Research Center (ECRC) was reviewed in 2005." The committee that took it under consideration was composed of international experts who approved the project, with the stipulation that Fred be the first director. He assumed the position in 2007.

It meant a *lot* of meetings. The endless talk and negotiations were necessary, but they grated on his nerves. Caustic remarks would just slip out, in a low grumble that was often (but not always) pitched just below the hearing range of whoever was speaking.

You also had to watch out when you asked him to write something about, say, the construction of a new building for Experimental and Clinical Research. Fred wrote, "Fruitful collaborations require a common ground and the ECRC building is ideal for that purpose. All aircraft carriers, battle ships, heavy cruisers, destroyers, gunboats, and other flagships… are represented at the ECRC. Thus, 'damn the torpedoes – full speed ahead!'" The text underwent some, ahem, minor editing prior to release.

Fred also hated the term "translational research." "What it sounds like is a method of translating basic findings into money as quickly as possible, and I suspected that the George W. Bush administration was behind the name. Indeed, that turns out to be the case. But," he bemoans, "I guess we're stuck with it."

Even seemingly innocuous requests could bring out the irony. When asked to translate the name of a physicians' organization (which shall remain nameless here), Fred wrote, "This organization is best translated as the 'Crooks, Gangsters and Union Toadies.' The entire group is superfluous and serves only functionaries and other people with inflated egos, who want to make good money without actually doing anything."

The MDC broke ground for a new "Berlin Institute of Medical Systems Biology," or BIMSB, which would host new groups and major new technology platforms. The aim was to create integrated, high-throughput platforms for DNA sequencing, mass spectrometry, drug screening in the test tube and cell cultures, and other methods.

In 2004, after having led the institute for 12 years, Detlev Ganten left to become director of the Charité clinics and medical school – one of the largest complexes of university clinics in Europe. It was a huge step: the Charité system employed 15,000 people and had a budget of a billion Euros.

Walter Birchmeier, a senior researcher in the institute's cancer program, was appointed acting director and then was confirmed as scientific director two years later. Walter was committed to pushing the institute's basic research activities to the highest possible standard. The strategy paid off handsomely: In 2010 a ranking service called Thomson Reuters, which compares the scientific impact of institutes, listed the MDC as 14th in the world in the fields of molecular biology and genetics. It was an extraordinary achievement for a center that hadn't yet seen its 20th birthday. But it didn't make things any easier for projects that had started in a doctor's office somewhere.

The institute kept trying to find a way to bridge the gap between such projects and work in the basic labs. Fred was doing it on a daily basis – through measures like helping set up and maintain the Clinical Research Center at the Charité, and a training program that brought MDs into research labs. If you wanted to change the scientific culture, and really integrate clinical and basic research, you had to start in the trenches.

But here work of Fred's group itself was an example of bridging the gap. It showed how difficult it actually was if you started with human subjects and wanted to expose a genetic disease mechanism, rather than the other way around. No one had any illusions about developing a cure for hypertension, but the project was going slowly. The pressure to obtain positive results was mounting, every time a scientific review committee came by to evaluate the institute's performance, or whenever budgets had to be allocated over the next funding period.

If the negative results continued, it was going to be hard to keep putting food on the table.

Philipp Maass had long been a familiar face in the lab. He kept showing up whenever he had a break in Tübingen. After finishing his undergraduate degree, and spending half a year in Australia, the time had finally come to apply for a position in a laboratory to do his doctorate. The only place that really interested him was Fred's group in Berlin. Fred's lab could take him on right away through the Charité medical school, and six months later Philipp was accepted into the PhD program at the Max Delbrück Center. That would cover the cost of his position for three years.

But it wouldn't necessarily pay for everything he wanted to do. While most of the group was focused on hypertension, Philipp decided to pursue the matter of brachydactyly. And even though no one considered short fingers a matter of grave concern to human health, he had very good reasons for his choice.

Part of the problem with hypertension was the fact that in spite of trips to Turkey, and three visits of the family to Berlin, Fred still didn't know where they ought to be looking in the body. "We'd ruled a lot of things out," he says, "but at some point, it would be nice to rule something *in*. The issue with the baroreflex was interesting – it's still interesting, we've had no reason to rule it out – but it was a bit like the hypertension itself. The autonomous nervous system is a big place. And except for a looping blood vessel in the brain, which we couldn't or weren't willing to experiment on, and more strange loops in vasculature throughout the body, we still couldn't establish a clear difference between the physiology of affected and nonaffected family members."

Well, there was one clear difference: in the skeleton and particularly the fingers and toes. They would be easier to study: first, you knew what part of the body to look at. Secondly, the development of body parts such as arms, hands, and fingers had been studied by molecular biologists for a long time.

By carrying out genetic engineering experiments such as *knockouts*, in which you removed a gene from an animal such as a mouse, scientists had discovered several molecules involved in the development of digits. If one of the genes in the locus on chromosome 12 was causing short fingers, you ought to be able to figure out which one it was. And if you were lucky, that might tell you something about hypertension as well.

Philipp came at the problem sideways, starting with another family that had the same type of brachydactyly as the family from Karamat. "The family lived in Potsdam, near Berlin, and had been recruited several years ago," Sylvia says. "But we hadn't gotten around to doing anything with their samples. Their DNA had been waiting in the fridge, and when Philipp was looking for a topic for his PhD thesis, we thought it would be a good project for him to take on."

The project had been initiated by Sigrid Tinschert, who had originally worked in the Human Genetics department at the Charité. Later Tinschert moved to the Technical University of Dresden but still came to the Charité in Berlin one day a week. In Dresden she found a second family with the same type of short fingers and recruited both groups into a study.

Her analysis revealed that both families had a disruption in DNA sequences on the short arm of chromosome 12. She knew about the project of Fred's group and thought the families might help identify the gene for brachydactyly in the Turkish patients.

Philipp had been working on his thesis for two years when he met Tinschert and talked to her about the second family. He decided to do some work on their condition alongside his dissertation.

Fred's group didn't have the manpower or resources to fully devote itself to another project in collaboration with the Tinschert lab. So he suggested that Philipp write a grant to the German Research Council, or DFG. That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would be a challenge – not quite on a par with suggesting that a student go off to Turkey for a year, but still a bit of hard work. Philipp had never written a grant application before.

But he managed to bring it to the point that it was ready to submit. The application went in to the DFG with Philipp's name at the top. Only then did he discover the requirement that DFG grants were only awarded to scientists who already had their PhDs – and Philipp was just beginning his. He couldn't believe that they would reject a grant, if it was good enough, just because a student had written it. So his name was excluded from the application's list and the grant went through.

The positive response allowed the group to put the necessary time, energy, and resources into the project. They went on investigating the family that Philipp had begun with, and later included the second family in Dresden with type E brachydactyly. "If you looked at the X-rays of their hands," Philipp says, "you wouldn't have been able to tell any difference between the German families."

There was one big difference, but it didn't have to do with hands – neither the Potsdam nor Dresden families had high blood pressure. Still… Something about all of these groups had to be the same, and at the moment Philipp decided to focus on the similarities rather than the differences. And who knew – short fingers and hypertension might, at some level, turn out to be two sides of the same coin.

It turned out to be another very smart decision.

Just a year before Philipp joined Fred's group for the long term, a lab at the Weatherall Institute of Molecular Medicine in Oxford (UK) discovered the first "brachydactyly" gene. The lab had started a project based on earlier findings that mutations in a gene called *HOXD13* could lead to the unusual development of fingers and toes. Some of these mutations caused two or more digits to be fused – either as separate sets of bones joined by skin, or as partial fusions of the bones as well.

In 2003, Andrew Wilkie's lab in Oxford carried out a screen of 128 people who exhibited a range of other hereditary limb abnormalities. The aim was to see whether other skeletal problems could be traced to mutations in HOXD13. They discovered that two individuals had an inversion in the gene, leading to brachydactyly. Others showed similar symptoms, but the cause was a mutation: a single change in the sequence of the gene.

Now Philipp wanted to determine whether a mutation or an inversion in the HOXD13 gene was also responsible for the short fingers of the Potsdam family. He carried out a number of experiments: First, he checked for mutations, and couldn't find any that distinguished affected family members from those without brachydactyly. By high-resolution karyotyping, using the FISH technique again, Tinschert's lab had found a chromosomal rearrangement even more dramatic than an inversion.

"In fact, for one of the probes, there were two distinct sets of signals," Philipp says. "One came from chromosome 8. But the other one appeared on chromosome 12. This meant that part of the chromosome 8 had *translocated* – it had jumped to another chromosome entirely."

It was exciting news, because it gave the scientists a handle to try to figure out the molecular cause of the family's brachydactyly. Maybe a crucial gene – or part of one – had been translocated from chromosome 8 or 12, to one of the new "translocation chromosomes." Or maybe the fragment that had been exchanged with chromosome 12 had landed in the middle of another gene, or disrupted its ability to function in some other way.

In rare cases, a translocation might also make a gene more active, by moving it to a place where it could be switched on by the control elements of another molecule. It might also be influenced by the overall "chromosome landscape" of its new environment, if it landed in a

place where large groups of genes were being activated or silenced.

"Regulatory elements 'above' or 'below' a gene sometimes come into physical proximity when strands of DNA create loops and are brought together," Philipp says. "This happens in different ways depending on the tissue that's involved. Protein mediators attached to the DNA help start the process of transcribing the gene, and for that to happen, various regions may need to be brought together."

He points out that although the same genetic information is present in every human cell – with a few exceptions, such as the immune system cells that produce antibodies – their activity changes from tissue to tissue. In each context, chromosomes behave in different ways to activate various regulatory pathways, and these determine the way a tissue develops and is maintained.

"Translocation events might cause regulatory elements on the same chromosome (a process called *cis regulation*) to become disrupted, and that causes the gene to become dysregulated," Philipp says. "Finding out would require discovering exactly what had been removed, and where it had been inserted," Philipp says. "So our next job was to look for the breakpoints – the edges of the sequence that had jumped, and the edges where it had been inserted."

They soon found that the fragment had landed in an extremely interesting place: on the short arm of chromosome 12, close to the location of the sequence that had been inverted in the Turkish family.

Philipp and his colleagues narrowed down the region of chromosome 8 that had been affected to a small amount of sequence – about 3000 base pairs. The translocation affected the internal architecture of a gene called *KCNB2*, affecting the arrangement of its protein-encoding exons and the non-coding introns found between them. The healthy form of the gene encodes a *potassium channel protein* – a protein that allows charged ions to pass through cell membranes, like the SUR2 molecule that the group had investigated before. KCNB2 is produced in the brain and in smooth muscle cells that line the intestine and help it contract during digestion.

That was interesting enough – any molecule found in smooth muscle might conceivably be linked to blood vessels and the regulation of blood pressure. But the family from Potsdam didn't have high blood pressure, and the Turkish family didn't show a disruption of chromosome 8.

Another important aspect of the situation was the fact that the family members from Potsdam had a second copy of chromosome 8 which was intact. (That was true of all the patients, including the Turkish family.) Philipp measured the amount of protein produced by the KCNB2 gene in their cells, and couldn't find a difference between affected and nonaffected family members. Additionally, he showed that *KCNB2* didn't play a role in cartilage formation. "So it clearly wasn't a very hot candidate gene," he says.

"What had happened on chromosome 12 was a lot more interesting," he says. "We discovered that the chromosome 8 fragment had been inserted a short ways 'upstream' of the gene PTHLH."

That immediately caught everyone's attention. PTHLH was the first gene that Sylvia, Thomas and their colleagues had investigated ten years earlier. At the time their first paper was published, it lay within the locus they had isolated in the Turkish family. Later, studies of the DNA from the families in America, South Africa, and elsewhere pushed it outside the region.

That original paper eliminated the gene because the scientists couldn't find any mutations that appeared only in the sequences of affected family members. Philipp found the same thing in the Potsdam family: PTHLH

hadn't undergone any significant mutations. But originally the lab hadn't been able to examine whether the control regions of PTHLH had been disrupted, by mutations or other problems such as the inversion. That couldn't be done if you didn't know the locations or sequences of the control elements.

Still, it was entirely possible – although they couldn't know this at the time – that the inversion in the Turkish family had separated PTHLH from those sequences so that the gene could no longer be properly regulated.

The insertion of a new DNA fragment near PTHLH might also affect the ability of control regions to influence the gene's activity. If that were the case, it would explain why two completely different types of DNA damage (the Turkish inversion and the Potsdam translocation) could have identical effects on fingers and the skeleton.

But was that really the case? Philipp was still interested in what had happened on chromosome 8. A computer analysis of the contents of the fragment that had jumped across revealed a pattern. The sequence seemed to contain a docking site for a protein called *C-ets-1* that acted as a *transcription factor*: in other words, by binding to DNA, it usually activated nearby genes.

The same type of analysis predicted that there ought to be another docking site for a family of transcription factors called *AP-1* on chromosome 12, very close to the region where the new fragment had been inserted. Other labs had shown that AP1 and C-ets-1 can regulate PTHLH. Philipp suggested that the borderline of the translocation downstream of PTHLH brought a regulatory C-ets-1 motif next to the AP-1 site. If that in fact had happened, C-ets-1 might now be docking onto the translocation in chromosome 12 instead of its normal site on chromosome 8. And there it might well have an influence on PTHLH.

If AP-1 normally docked onto the site, its activity might have changed because of the translocation. So far, however, these were just hypotheses generated by a computer, and they needed to be tested. That could be done through experiments in the test tube, where the DNA would be exposed to the transcription factors to see if they would bind.

It would be far better, though, to demonstrate the effect in patients' cells – as well as to show that these events had some sort of effect on the development of bones.

Why do people develop short fingers, or longer ones? The answer lies in the prehistory of a human life: in events that occur between the fertilization of an egg cell and the production of a fully-formed human being nine months later, and continue over its development into an adult.

The fertilized egg is a *totipotent* cell, able to develop into any of the types found in a human body. The first few divisions produce *embryonic stem cells*, which are still pluripotent, but they divide again to produce three types of tissue called the three *germ layers*. One of these types, *mesenchymal* stem cells, go on to specialize even further into *osteoblasts* (that produce bone), *chondrocytes* (cartilage), *adipocytes* (fat cells) and smooth muscle cells.

The reasons for the unusual development of fingers and the skeleton of the families in Potsdam and Turkey probably lay in processes within chondrocytes. And somehow those processes had to depend on the only significant change that had been discovered in the families' DNA: a disruption in the short arm of chromosome 12. Philipp's project indicated that it probably involved the PTHLH gene.

But proving this would require obtaining chondrocytes or other specific types of cells from affected individuals, and that wasn't going to be easy. Such cells are most common during the periods when the body is most actively growing – in the early embryo, or during childhood.

Even then, they are a minority among cells in the bone, are hard to isolate, and are hard to grow in laboratory cell cultures.

Fortunately, modern stem cell research provides a partial solution: Scientists have found ways to take cells that have already differentiated and prompt them to change types. Much of this work involves *fibroblasts*, which are found in the skin and are involved in processes like wound healing. The scientists used patient and control cells to measure the amounts of RNA produced by the PTHLH gene. They couldn't find any significant difference in the brachydactyly patients.

This didn't yet exclude PTHLH, because it is involved in the development of several different organs and is essential in different body tissues. Philipp thought that *PTHLH* might only be dysregulated in chondrocytes – but finding out would require obtaining cartilage from the patients.

"Fred suggested we should go skiing with the patients," he laughs. "Somebody might have an accident and require knee surgery, which would give us a chance to obtain cartilage."

Well, that didn't sound very likely, so Philipp decided to take another approach. "In recent years scientists had found ways to transform one type of cell into another, by exposing them to transcription factors and other molecules that would stimulate their development along a different path," he says. "So I learned to turn fibroblasts into chondrocytes, which would allow us to investigate the behavior of the PTHLH gene in the particular type of cell we were interested in."

To achieve the transfection of the cells, the lab relied on the help of Yvette Wefeld-Neuenfeld, who had officially joined the lab around the time Herbert Schuster left. But they had all known her much longer; she had worked with the group in some capacity since the mid-1990s. Her academic history reminds me of Atakan Aydin's; both had attended the Realschule, then worked hard to continue their education. In Yvette's case, ten years of experience in a research lab convinced the college to accept her.

"After school I got training as a medical technician," Yvette says, "and to get experience I worked in the lab in the Franz-Volhard Clinic for several months as an unpaid volunteer. In 1994 I was given a position as a technician by Hermann Haller, a colleague of Fred Luft's." She was impressed that Fred and Hermann appeared from time to time with chocolate cake and coffee and took time to chat with the group.

When she suffered a lung injury and had to spend three weeks in the hospital, the physicians took time out from their busy schedules to visit and check on her progress. After her recovery, Hermann sent her for advanced training in Heidelberg and Basel (Switzerland), but she wanted to come back to Berlin. She worked for a while in the company Infogen, which Herbert Schuster had launched, but when Fred and Sylvia offered her a technician's position in the lab at the MDC, she jumped at the chance. Over several years she has juggled the requirements of the job with her role as a single mother.

Later Sylvia and the others encouraged her to go to the university, and in 2007 she received a degree in Biotechnology from the Technical University of Berlin. "It was very molecular-biology oriented, and it was a lot of work," Yvette says, "but I kept working with Sylvia and the lab on the weekends."

Following graduation she rejoined the lab on a full-time basis; one of her projects was to investigate the locus on chromosome 12 in the Turkish family. Even though the genes in the region didn't seem to be involved, the inverted area contained several *expressed sequence tags*, or ESTs: DNA sequences that were being transcribed into RNA molecules.

Those RNAs might not encode proteins, but over the past decade, researchers had discovered that the molecules had many other functions. In fact, a huge amount of the human DNA sequence was used to make the molecules. Some of them had an influence on whether other RNAs were actually used to make proteins.

Researchers quickly turned this knowledge into a powerful technology to manipulate the activity of genes. They even began experimenting with a method of using RNA molecules as treatments for a few genetic diseases.

It was one of those discoveries that originated in the most unlikely of places: an attempt to enhance the color of a flower. In the late 1980s, a scientist at a California company called Advanced Genetic Sciences, Inc., did an experiment in which he hoped to create a more vivid purple color in petunias.

Adding a second copy of a gene often strengthens a trait in an organism, so Richard Jorgensen added a duplicate of the gene for purple coloring into the petunia genome. The outcome was a great surprise: many of the seeds produced flowers with petals that were completely white.

Somehow the second copy of the gene was suppressing the first. At first Jorgensen and Carolyn Napoli, his wife and collaborator, thought this effect might be peculiar to petunias. But soon researchers working with other plants and animals discovered the same effect, and that RNA molecules were responsible. If an organism's cells produced a messenger RNA molecule, and you managed to slip them a *complementary* RNA molecule, you could often prevent the original mRNA from being used to make proteins.

This effect was based on the fact that RNAs are basically built of the same stuff as DNA – *nucleotides*. The complementarity of nucleotide bases in DNA (A binds to T, and C binds to G) is what creates the double helix, and two complementary RNA molecules will bind to each other as well to make a double strand. This often leads to the destruction of the molecules before they are used to synthesize proteins.

Over the next few years researchers discovered that you didn't have to insert an entire complementary RNA molecule to get the effect; you could often achieve it just as well by adding a *small interfering RNA* (siRNA) which covered one critical region of the molecule. They developed this principle into a new method of "knocking out" genes by injecting cells or organisms with siRNAs.

Then scientists discovered that all sorts of cells make their own "interfering" RNAs – and they are even much smaller. Such *microRNAs* dock onto regions of messenger RNAs and activate a cellular machinery that slices up the molecules. Today we know that this is a very widespread phenomenon. A huge amount of DNA that was formerly considered "junk" is now known to produce microRNA molecules that play a crucial role in shaping the population of proteins in cells.

Some of the "junk" is made into longer RNAs as well. The cell assembles single messenger RNAs out of fragments of genes (exons) scattered out over long distances in our DNA sequences, and it can also read segments of DNA to assemble longer RNAs that don't encode proteins. These molecules are called *long noncoding RNAs*, or lncRNAs, and their functions in cells mostly remain a mystery.

So the inversion sequence in the Turkish family might not cause a problem directly for a gene at all. The disturbance might involve microRNAs, or lncRNAs, and Yvette Wefeld-Neuenfeld and other members of the lab spent a long time looking for them.

This process had become much easier over the years since Herbert and Sylvia and Fred's team had done their first DNA sequencing. The machines had become much

Yvette Wefeld-Neuenfeld

faster and more accurate, and overall, researchers had learned a lot about the information encoded in sequences. This led to improvements in the programs that computers used to search for bits of DNA that were transformed into RNAs. "Deep sequencing" projects were now able to detect tiny RNA molecules, even those produced in very small quantities.

And techniques such as *mass spectrometry* had made great strides at carrying out a sort of global census of cellular proteins. This method uses enzymes to cut proteins into tiny fragments and then fires them past a magnet; the fragments fall into a detector, which basically weighs them. Since the amino acids that make up proteins have different chemistries, they have different electrostatic charges, and the magnet bends them in different ways depending on their composition. The size and charge of a fragment determines where it falls, and a computer program can use this position to figure out the amino acids that compose it. With that information, the computer can scan the human genome sequence to find a unique code – a gene – that matches the entire recipe.

Information from all of these types of experiments was entered into public databases, where it could be retrieved. So if somewhere a lab had discovered an RNA or a protein produced by the sequence in chromosome 12, Fred's lab had a good chance of finding it.

Compiling all of that information with smart gene- and RNA-detection software now gave the group much better chances of finding functional information in the sequences that had been disrupted in the Turkish and German families.

But once again, that information would only be meaningful if the team could find a difference in the molecules produced by certain types of cells: They needed finger-building cells from affected and nonaffected family members.

Philipp and Yvette were learning to turn fibroblasts into chondrocytes. They got the fibroblasts from patients' skin, and then raised them over a period of two to four weeks in a complex chemical broth. Complex is putting it lightly; to get a real impression of the process, here's how Philipp put it in his paper:

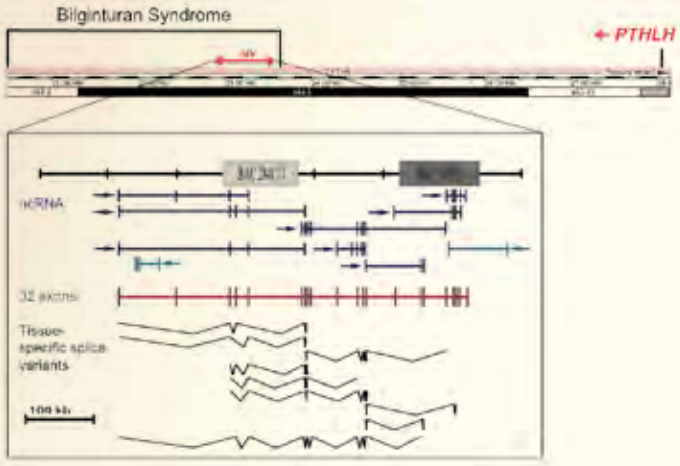
> *"The chondrogenic differentiation of fibroblasts was done in pellet culture with DMEM, supplemented with 10% FCS, 100 U/ml penicillin, 100 mg/ml streptomycin, 1xITS-X (Invitrogen), 10 ng/ml hTGF-b1 (R&D Systems), 500 ng/ml rhIGF-1 (R&D Systems), 50 mM scorbate-2-phosphate (Sigma) and L-glutamine (PAA), for 14–28 days."*

And if you can understand that, you can probably do the experiment yourself.

It took several tries; finally, after 3 weeks of working in three-dimensional cell cultures, the scientists discovered small "pearl-like" clusters of cells that were the sign of cartilage tissue. Now they extracted RNAs to measure whether PTHLH behaved differently in the chondrocytes of people with brachydactyly type E and their nonaffected relatives. "We had our fingers crossed," Philipp says. "*Tightly* crossed, because a group at the New York University School of Medicine, had just established a link between PTHLH and the growth of the skeleton."

The scientists found that in the patients, PTHLH RNA was being produced in lower than normal amounts. "Although the role of PTHLH during chondrogenesis was known," Philipp says, "this linked the molecule to brachydactyly for the first time."

They also found that affected individuals produced lower amounts of PTHLH and other proteins: ADAMTS-7 and a related molecule called ADAMTS-12, two protein-cutting enzymes that are directly controlled by the PTHLH protein. In other words, since the cells



The DNA sequence in the inverted region of the locus for Bilginturan's syndrome contains exons (vertical marks on the red line) that are combined in different ways to create non-coding RNAs in different tissues (blue lines). Two of these variants do not appear in people affected by Bilginturan's syndrome.

didn't make as much PTHLH, the genes that it switched on weren't being activated at normal levels.

And they could trace the causal chain to even earlier events. The DNA sequences that had jumped across from chromosome 8 provided a docking site for the C-ets-1 protein. In the healthy chromosome 12 – without the translocation – AP-1 would normally bind in front of the PTHLH gene and activate it at a high level. With both binding sites, AP-1 and C-ets-1 could both dock in front of the gene. When that happened, C-ets-1 was tuning down the transcription of RNA from PTHLH.

Philipp and the lab now had a full story. A disruption in the DNA of chromosome 12 was switching off the production of a protein that was crucial to the development of cartilage and possibly bone. They had discovered the molecular basis of short fingers in the family from Potsdam.

Meanwhile, Sylvia and Yvette and their colleagues were looking at fibroblasts from the Turkish patients. Searches of the databases revealed five ESTs – signs that sequences from the locus on chromosome 12 produced RNAs, discovered in experiments by other groups. Were those regions being used differently in affected and nonaffected individuals?

"Looking at different versions of the inversion had allowed us to narrow the locus down to a region that contained no known genes," Sylvia says. "But it might contain a microRNA, or some other type of RNA that didn't encode proteins."

To find out, the group began with material taken from healthy subjects: from the brain, aorta, and cartilage. They used PCR to copy DNA sequences near the ESTs and search for any RNAs that might be produced.

Sylvia and her colleagues discovered that the region contained a much richer array of sequences that were transcribed into RNAs, raising the number of ESTs. Cells in different tissues used them in different ways: "splicing" the RNAs into different forms containing different sets of the 32 exons. All of them were "noncoding". "None had the features necessary for translation into proteins," Sylvia says. "The largest molecule would have been only 80 amino acids long."

Atakan carried out experiments in the test tube and showed that, in fact, the RNAs weren't being made into proteins. The next task was to look at the fibroblasts taken from the Turkish family – were the cells of affected individuals producing different versions of the RNAs than those of their unaffected relatives?

"We found two types of RNA – different combinations of the EST sequences – that were only produced in nonaffected people," Sylvia says. "That was surprising. Those who are affected have a second copy of chromo-

some 12 with the healthy version of the chromosome. But we couldn't detect any RNA from that chromosome in the fibroblasts."

This might be a microRNA, used to block the use of some other RNA in the cell. If so, it wasn't working in the affected people – at least not in their fibroblasts. Atakan and Regina Uhlmann developed methods to detect microRNAs from human tissues. So far, the group had no idea what genes the microRNA might be blocking. They needed to develop other types of cells – chondrocytes, or better, the even more basic mesenchymal cells that they arise from.

The group turned to another method, called *stable isotope labeling by amino acids in cell culture* (SILAC), to try to identify potential target genes. Here they had the help of the MDC lab of Matthias Selbach, world leaders in the method. This approach relies on growing cells in a standard culture medium, and then moving them to another. The amino acids in the new medium – which will be used to build new proteins starting at the time the cells are transferred – are "heavy" because their atoms have extra neutrons.

The mass spectrometry method can detect the difference between the two types of amino acids. So scientists can track the speed at which proteins from the old medium are degraded and new ones are constructed in the second medium.

They discovered that fibroblasts from the patients, which weren't able to produce the noncoding molecule, showed differences in a number of genes whose activation depends on a molecule called *TGF-beta*.

"The proteins in this pathway are known from human syndromes involving tangled blood vessels," Sylvia says. "So once again, there was a reasonable connection to hypertension. But to learn more, we needed to obtain more types of cells from the patients to be sure that this was happening."

Fred had begun planning another trip to Turkey. It would provide another chance to obtain cells – this time, the group was hoping to capture endothelial progenitor cells from the blood samples they took. Somewhere within those cells, the scientists believed, they would find the ultimate cause of Bilginturan's syndrome.

19 Priest, President, Philosopher, Poet

There we stood, a bedraggled band in the airport in Trabzon, waiting for our luggage to appear. First came two huge, black suitcases, which weren't as heavy as they looked as we pulled them off the conveyor belt. We loaded them onto luggage carts along with some of the other bags. Up came the three locker-sized metal boxes with the medical supplies. In their wake I saw a small silver key, drifting along by itself, and I wondered whom it belonged to.

The customs officials headed for the silver boxes. I pushed a cart with one of the big suitcases piled under a heap of other bags and Philipp took the other. He put his camera bag on top and held it steady with a hand.

I was tired from the two flights and hesitated before the automatic doors, with an instinctive terror of international borders. "Just go on through," Philipp said quietly. "Don't stop, just push it through."

Okan was talking to the officials about the metal boxes. Two of them had already been opened and inspected; the customs officers saw a neat array of blood-pressure equipment, empty sample tubes, and other medical supplies. Suspicious but nothing actionable.

Atakan and Cafer

The third case interested them the most, because they were having trouble getting it open.

Fred, Okan, Atakan, and Sylvia searched their pockets and shrugged. The key had mysteriously disappeared.

I thought about saying I'd seen such a key, but when in a foreign land, when in doubt, it's never a mistake to keep your mouth shut. And Philipp was nudging me along.

Now everyone's attention was focused on the third box. Two of the officers consulted a superior who said brusquely, "Open it," and they found a pry bar that they applied to the latch to force it open, breaking the lock. They seemed disappointed to find nothing but another batch of interesting but perfectly legal medical supplies.

Maj Britt Hansen wheeled her suitcase through the customs; no one stopped to check the camera equipment in her backpack. She joined Philipp and me to wait for the others.

"What's with the suitcases?" I asked him.

Philipp did his impression of the Mona Lisa. Later I found out we had wheeled a couple of hundred boxes of blood pressure medication donated by Astra Zeneca across the border into Turkey. True, Fred had official-looking letters from the pharmaceutical company and the Charité to accompany the several hundred little boxes of drugs – even if they had picked us out for inspection, we wouldn't have languished in a Turkish prison. At least not for very long.

I was glad I hadn't known in advance. I would have been terrified.

But nobody had paid any attention to the suitcases. Everyone had been too occupied with the metal box, and its lost key.

Outside the customs area, we ran into about a hundred women covered completely from head to toe; the only parts of their bodies visible were the tips of their fingers and their eyes through narrow slits in the cloth on their heads. Cafer and Mehmet and another man were waiting outside, but they didn't know us and we didn't know them; then Okan came through and greeted them like long-lost brothers. That's practically what they were, given the year he had spent with the family. Philipp, Maj Britt and I were along for the first time, so introductions were made all around. The third man served as mayor of the largest town near Karamat.

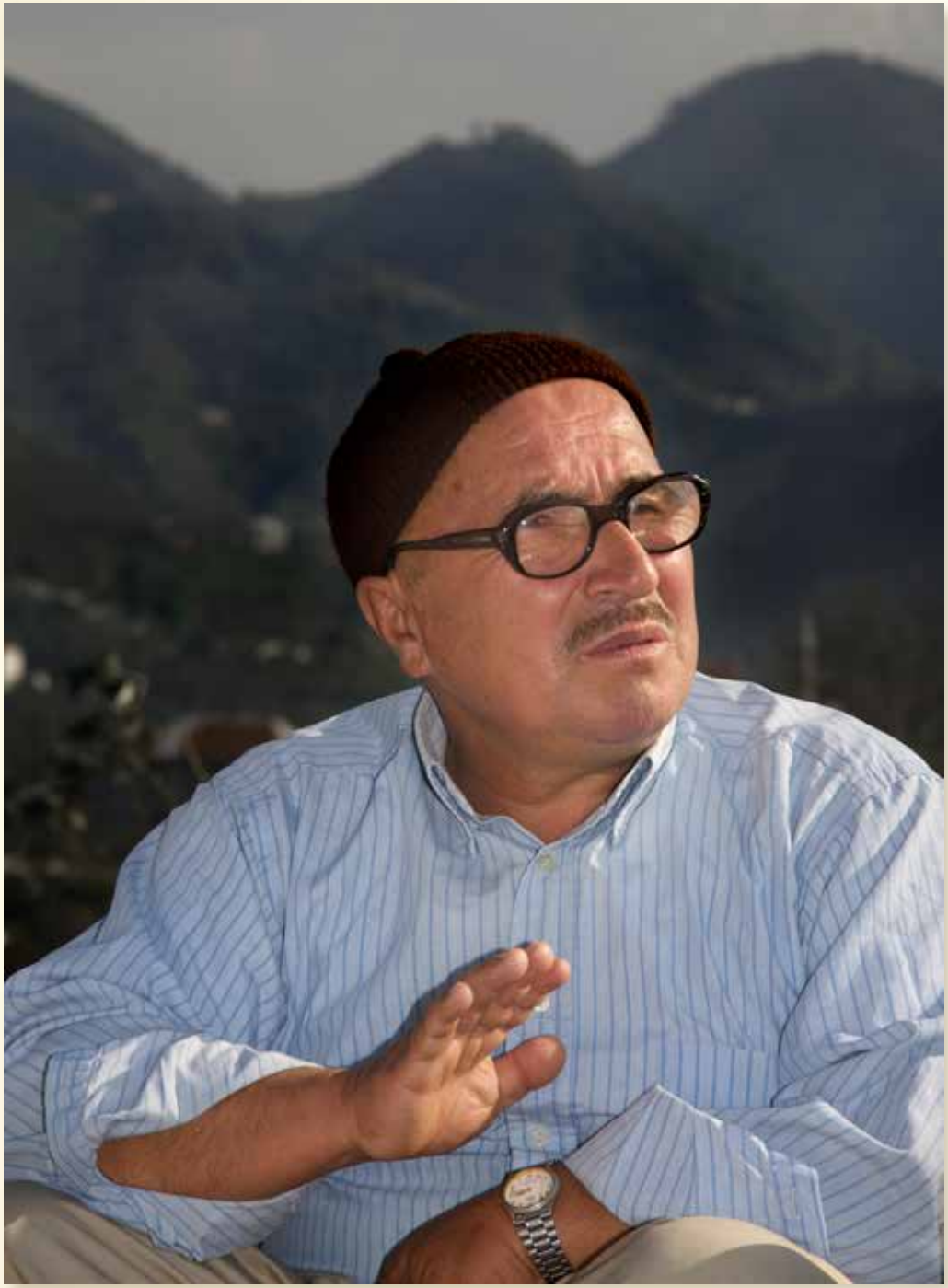
Outside a big red van was waiting. It was October, early evening, but the air wasn't nearly as brisk as it had been that morning upon our departure from Berlin. The big silver boxes went in first, and we piled everything on top and climbed in for an hour-and-a-half ride to our hotel. As Mehmet drove I got my first look at the hands of an affected person – the hands that were, in a way, half of the reason we had come. I noticed the short span between his wrists and knuckles, the way his fingers curled around the wheel as he drove the big vehicle at a smooth, even pace along the highway.

"Fifteen years ago this road wasn't here," Fred remarked.

"You had to drive through every little village along the coast," Okan said. "That was a lot of fun, especially when there was a market. Then they built this highway, it stretches all along the Black Sea, from Georgia practically to Istanbul. The towns were all crammed up against the water, so they had to extend the coast by pouring in stones and concrete."

He carried out an animated conversation with Cafer all the way. There had been a few snags during the trip preparation, on both sides, and he translated from time to time.

"There's a whole part of the family that may not participate," Okan said. "Ali is upset for some reason. We'll have to talk to them."



Sylvia asked about the group that lived in another town, the branch Thomas had discovered by surprise in his interviews.

"They're in," Okan said. "In fact, they were the first ones I got in touch with. I found them on Facebook." He said he had finally made a Facebook page after e-mails from acquaintances with their own pages finally got annoying. One of his new "friends" was a young man he'd met from the drug study, from the separate branch of the family.

"He was 14 years old the year I was there," Okan said. "So I wrote him and said, 'Remember me? I'm trying to organize a new trip, and we'll come and see you and the rest of the family again. I've lost Cafer's phone number. Could you help me out and give it to me?' He wrote back and said, 'Sure, Okan, of course I remember you and I'd really like to help – but who's Cafer???'"

The only real contact between these branches of the family had come during the group's first visit and then Okan's year; they still didn't feel very related. Okan wrote back: "You met him when I was there… just ask your mom. She'll probably have his number." And she did.

The highway gleamed under rows of high floodlights that highlighted the crests of waves across the dark water. Somewhere along the way Mehmet pulled over at a low, hut-like structure: the local equivalent of a rest stop. We sat down at wooden tables outside. Okan ordered black tea and finger food – cheese sticks and hazelnuts – and he translated as the mayor talked a little about village life.

"The arrival of technology is making life easier," the mayor said. "Thirty-five years ago the small towns on the coast were luxurious compared to the villages, which didn't even have electricity. Now they do, and TV, and Internet."

People no longer have to leave the region to find a job, he said. "There's a university in Trabzon, even a hospital where they can work if they become doctors or nurses… So they don't have to leave anymore. There are big companies that process the nuts and tea. Eighty percent of the world's hazelnuts come from the Black Sea coast."

He picked up one to show what's special. "They have an outer shell, and if you crack it, there is a skin over the nut. The quality is determined by the fact that in nuts grown here, the skin slips off very easily. Other nuts, it sticks, and you have to process them a lot.

"What we love about this place is that it's natural," he said. "It's a simple life, sitting in nature, looking at the ocean, and just living. It's a feeling… Something you don't have in the city."

The farmers' life is hard, he said, alternating between their homes in the village during the harvests and escaping to the Yayla when it gets hot. In the winter many of the older people move in with relatives in towns or the city. I asked him if they have to work while they are there.

"What they earn is usually enough," he said, "and the older ones get a pension. Now you usually have at least one or two people in the family with pension money."

Another change, now that more of the older family members were surviving to benefit from their pensions. The arrival of science and medicine – first on the backs of two mules, and now in the back of a big red van – had directly improved not only the health of the family, but greatly changed their economy and lifestyle. So far, this hadn't upset the things they cherished most.

Later we checked into a modern hotel beside a bay full of colorful fishing trawlers. We agreed to meet later for a glass of wine. Fred got his key first and whisked off to his room. A few minutes later he was back at the reception desk.

"The beer in the mini-bar is warm," he growled.

Philipp and I went to investigate. The rooms had those key-cards that you had to plug in just inside the door to activate the electricity. Without a card, the refrigerator in the room shut itself down. We filled the sink in Fred's room full of cold water and put the beer in it. Then I went out to try to find a shop to buy beer, which involved crossing a pedestrian bridge, built over the highway to get to a small commercial street. Most of the convenience stores didn't sell alcohol, befitting a region with no tourists and a population that seemed to take their religion seriously, but I finally found a place on the corner with brown bottles that were mildly cool. It was impossible to communicate with the two men in the shop, but sign language never fails if all you need to do is buy beer.

When I returned, Fred was standing at the reception desk again. "The Internet doesn't work," he said, so Atakan went up to get his WLAN going.

In the morning we had a big breakfast of bread, cake, strong cheese, and coffee. Then Cafer appeared with the van again. The morning fog began to clear as we loaded up and headed for our first stop: the hospital in Samsun.

"We need to get them to agree to let us handle our blood samples here," Okan said. "Problem is, we don't have a letter giving us official permission to do the work. Back in the early summer, we started sending letters and trying to get the responsible officials on the phone. Then things got pushed into another dimension: Turkish bureaucracy. I kept reaching people who said, 'You know, I'm not really the person to ask.'"

This time the group wanted to take biopsies, which required a special type of permission. "To obtain that, we contacted yet another official – who also turned out to be not the right one," Okan said. "He gave us a telephone number, and I said, 'Okay, is the person who needs it in your building?' Yes, just one floor up. I said, 'Well, would it be possible for you to personally take the letter I sent you and give it to him directly?' Sure. So several days later I called the person, who was in fact responsible and said, 'Did you get my letter?' 'Which letter?'

"Somehow six different departments have gotten involved in this thing. We still don't know what our official status is."

"It's like what his brother went through during his internship in the U.S.," Fred said. "Even if all you want to do is get blood samples, there are so many official and ethical hoops to jump through that you never know if what you are doing is strictly legal. This is the kind of thing you encounter all the time when you try to do studies across national borders. Genetic syndromes are international, but medical work operates within each different system."

We took an elevator to the top floor of the building for a meeting with one of the hospital's directors, who had a huge, penthouse-style office overlooking the sea. Fred, Okan, and Cafer sat across from his desk. The rest of us took the back row, feeling like we'd been assigned to the children's table at a dinner party. All the scientists needed at the hospital was to freeze blood samples, but even that might be asking too much. Okan presented letters and a lengthy explanation of what was going on. Cafer spoke up. The official studied the paperwork, summoned an aide, and stroked his thin mustache unhappily.

There were procedures to follow, he said stiffly.

They had tried, Okan said, and launched into a long account of his letter campaign.

After about an hour of this, some of us left as the negotiations continued. We took the elevator down to the lobby. There was no canteen, but people had set up vans and small tents in the parking lot, where they sold soda, candy, and tea in thin plastic cups that you couldn't carry without burning your hands.

"He's just upset that he doesn't have much power over this," Atakan said. "This guy is a big-shot, and he feels he ought to have the right to say yes or no. But here we are, it's an accomplished fact, and he can't very well refuse."

When the others finally emerged, they said the director needed more time before giving the work his blessing. He would review the materials; Fred and Okan should come back later in the week. But there was no time to wait around, and nobody had any desire for another meeting like this. So it was back into the van, for a rugged drive into the hills.

Later we discovered that after our departure, he placed a call to the national health ministry and raised questions about the project and its intentions. In a way it was understandable; it wouldn't have been the first time a group of Western researchers arrived in Turkey and used and abused the population for some obscure scientific purpose. Once they published their papers, they were rarely heard from again.

About a year before our trip, I had talked seriously with Fred about doing a book on the Turkish project. I had already written a long feature story about the work, but twenty pages only scratched the surface. The project was moving forward, and there seemed to be enough for a much longer story… I had no idea.

The book project, plus the recent progress in the investigation of the Dresden family and the work on the inversion, made Fred start thinking of another trip to the Black Sea. There followed all the months of planning – including the failure to get definitive approval for a project that had been approved many times before. The situation still hadn't been resolved, and that was going to haunt the group later in the week.

There was no way to remember the forking, twisted route that Cafer followed, but finally we arrived at his house – a yellow, two-story structure atop a hill, with a magnificent view of the sea and the steep hills that climbed steadily inland. We parked on the broad terrace and Cafer opened the back door. We unloaded the boxes and kicked off our shoes at the bottom of the stairs before carrying them inside.

There was already an impressive collection of shoes outside.

The original plan had been to work with the family in the new mosque that had been built – thanks to Cafer's efforts, with a small contribution from the scientists – but for some reason we'd be doing it at Cafer's place instead. It was the same house Bilginturan had stayed in during his first trip 40 years ago, but an extra floor with several rooms had been added on. The prayer house had been demolished, so the makeshift hospital would be installed at various stations through the house.

The most striking thing about the place was the number of floral patterns: on the sofas, the curtains, anything made of fabric. The women's dresses and scarves were equally ornamented. Later we found out that neither Cafer nor most of his relatives required their daughters to wear headscarves, but both of his girls and his wife did.

The house smelled vaguely of cooking. We met Cafer's wife and his two daughters; we'd already been introduced to his son, whom we had picked up on our way up from town. The two oldest children had been very small during Okan's drug study; I had seen pictures of him with them both on his lap, taken during the first trip to Turkey. Now they were in their late teens. The second daughter was fourteen, and had been born sometime after the 1994 trip.

After unloading the equipment and the obligatory round of black tea, we climbed back into the van to drive to Ali's house. More twists and turns along the gravel roads. I was looking forward to meeting the "musketeer" who had been thrown in prison during the drug study. Okan needed to convince the old man and his family to participate – Ali and several of his children were affected – but wasn't sure he would succeed.

"Somehow, we think, they got the impression that we were giving money to Cafer's family, while all we have done is cover the costs of renting the van," Okan said. "Or there's some other rumor going around. In any case there's a bit of tension, and we need to try to smooth things over."

Ali's home was several kilometers away, tucked into a niche on the side of a hill. Mehmet parked at the bottom and we walked up a grassy pathway. Ali appeared at the doorway – a tiny, plump man in thick bifocals, a short-sleeved shirt, and a white prayer cap called a *takke*. His wife wore a long-sleeved purple sweater and on her head, a red shawl with white embroidery.

Ali greeted Okan warmly, taking him in his arms, and welcomed us inside. There, surprise surprise, we were served tea. And hazelnuts. And cookies. We sat in a circle on couches, in a cozy living room with a cooking area on one side, and a tall cabinet that held patterned dishes and pots and pans tidily arranged on shelves above the sink. There was also a blood pressure gauge that Herbert Schuster had given Ali a long time ago. It was a wrist cuff, and it didn't work anymore. Okan promised to give Ali a new one with an arm cuff before we left. "I left six or seven here with the family after the drug study," he said.

Okan engaged Ali in a long discussion – partly catching up, partly explaining the purpose of the current visit. He said that we had set up our "base" at Cafer's house and hoped that Ali would come by sometime later in the week.

Ali was one of Kemal's brothers, and was currently the oldest living member of the family with Bilginturan's syndrome. From the beginning, he had accompanied Kemal on trips to various doctors and had become a driving force in the family to find help in understanding and coping with the problem. He had had contact with Nihat Bilginturan several times over the years – initially because of problems with his heart; the Turkish pediatrician had referred him to cardiologists in Ankara and elsewhere. In the late 1980s he had suffered a heart attack and endured several stays in the hospital, as well as stays in the clinic in Berlin.

"Initially he was very hopeful," Okan told me later, "but now he has become rather pessimistic. All these years have passed. He has health insurance, so his hypertension has been treated – partly as an aspect of therapy involving his heart problems."

Ali said that initially, family members hadn't been aware of the condition or connected their problems to hypertension. Earlier, a lot of people died at a young age anyway. But once it became clear that something serious was going on, a few like Ali wondered, "Why do we have this? Why us?" "And that has really occupied his thoughts over the past forty years or so," Okan said. "When a relative had a stroke, they wondered whether other scientists somewhere might know why something was wrong, and if they were really unique in the world? But most people weren't really too occupied with it; they just accepted it. 'That's the way it is,'" Okan paraphrased, "and they just went on with their lives."

Ali had been instrumental in encouraging the family to participate during the first visit in 1994. After Hakan and his relative in Turkey had managed to establish contact with Bilginturan, the pediatrician called up Ali. Some scientists from Germany wanted to visit the family, Bilginturan had said, and their intentions seemed proper. "Of course," Ali had said, "let them come."

Now Okan told him I planned to write a book about the project. I had heard the story of his misadventure with the musket. Did he still have his grandfather's weapon? Could we see it? Ali beamed and whisked off to a neighboring room.

In the meantime, a neighbor had arrived at the house about the same time – a distant relative of the family and a resident of the village – and greeted Ali's wife and Okan

as he came inside. He wasn't as old as Ali; I guessed he might be in his early fifties, but he didn't seem to be in very good shape. He leaned on a cane as he scuffed across the room, and the pain was obvious as he carefully lowered himself onto one of the couches.

He was the first of many neighbors or relatives who would appear during the week; they'd heard that doctors were coming – perhaps they could help with a complaint? In this case things were serious. Fred and Okan seemed to be reading each other's minds as they peppered him with questions, following a finely tuned flow chart in their heads to home in on a tentative diagnosis. It was like listening to two violinists perform a duet: Distal? Yes, distal. Started at what age? About 29 or 30. Bilateral, the condition has progressed very slowly. No one else in the family has it. Some sort of peripheral neuropathy. He had been investigated at the hospital in Istanbul, but no definitive cause had been established. He was losing feeling in his legs, and the problem was creeping upwards. Then Ali returned with his guns.

He was carrying a shotgun and a pistol. The shotgun was newer than the musket that had belonged to his grandfather and been thrown out a window fourteen years before. "Quite an adventure," Okan laughed, as Ali handed him the weapon.

"For me, too," Ali said.

The pistol was a 9 millimeter, Okan said, the kind used by the Turkish police. He examined it and passed it along to Mehmet, who scowled.

"Why don't you have the safety on?" he demanded, and fiddled with the catch at the top of the grip. I had a sudden vision of a doctor blasting a hole in the ceiling, or worse.

"You have a license now?" Okan asked.

But of course, Ali beamed. He disappeared again and returned almost instantly with a small plastic card that he proudly passed around. Fred raised his eyebrows when he saw the picture. "Good resemblance," he muttered. Okan took a look.

"It's his son's," he laughed.

Ali explained that he was a peaceful man who never sought conflict with anybody. No harm ever came from his weapons, but you had to be prepared to take care of yourself and your family. "Like in America," he said. And then there were the wild boars. Most of the time all you had to do was fire off a shot and they would disappear.

When I met Okan's brother a couple of months later, Hakan told me that once he had been riding in the country with Mehmet at the wheel of the jeep. Suddenly the little man pulled his gun, stretched his arm directly in front of Hakan's face, and fired off a shot through the passenger seat window. Hakan had lurched back in the seat, startled, his ears ringing.

"A boar," Mehmet told him calmly, and kept driving as if nothing had happened.

Now Okan said, "If you have a gun license, you have to pay an annual tax. So about 80 percent of the people don't have them."

"I had one," Ali said, "but I needed the money, so I sold it."

Before we left, he promised Okan that he would come to Cafer's place on Saturday.

The drives up and down the hills were times for talk. Mehmet pointed out features in the landscape and talked about growing up on the farms. The families made their income from the hazelnuts and tea. They didn't use any chemicals on the crops; for fertilizer they used dung from the sheep. The hazelnut shells also make good compost.

He pointed out a patch of gourds and later, at the house, showed me a yellow one about the length of his arm. "In the old times people used to make holes in them and carry water in them," he said.

He said the families raised a small number of animals, along with kiwis and a few other "exotic" crops, for their own needs. Between May and September it got hot on the coast and they drove their animals up to the Yayla. It was much more comfortable; the nights were cooler; there were fewer insects to bother the animals, which produced better milk up there.

For children the hike into the mountains was a big adventure, but once they arrived everyone faced a lot of hard work. Mehmet estimated that the community had about 100 sheep and 20 cows. The sheep had to be shorn, the cows milked, and the children had to help with everything.

"When I was a child," Mehmet said, "I thought about how steep everything was here. I wondered what it would be like to live in the city. I tried to imagine living in a place where everything was so flat, and where there were no trees. How strange that would be. It seemed exciting. Later I went to school there and realized it wasn't so exciting after all.

"It was the same way with sweets," he said. "During my childhood there was one shop here, and they sold cookies, and I wondered why the adults didn't want to eat them. They tasted so good. Now I'm an adult and I don't eat them any more. It's the same thing."

"Mehmet is always thinking," one of the women in the seat behind him said. "You know his nickname? We call him the 'President.'"

Mehmet laughed.

"It's because of the first time his father took him to school to register him," the woman continued. "He told the school master, 'Take good care of my child, because he will be President one day.' And Mehmet finished school, and so now we call him the President."

During the days he drove us around, I often found Mehmet standing quietly beside the van, smoking a cigarette, stoically quiet. "You don't talk much," I said, wondering what he was thinking about.

"It's because they never listen to me anyway," he laughed, and stamped out the cigarette on the pavement of the terrace.

Another subject during the drives was science; Sylvia and Philipp and Fred caught Okan up on some of the leads they had followed over the past few years, only to wind up at dead ends.

"The SOX5 gene, which has been implicated in the development of the cartilage and the skeleton, isn't too far away from the linkage region on chromosome 12," Philipp said. "We spent some time on that one."

"I was pregnant and one day I got a call from America, from a group in Houston, saying they'd found 'our' gene," Sylvia said. "They'd discovered that it produces a long form of a protein in mice; if the animals don't have it, there's a skeletal phenotype. The mice are unusually small." So the group had chased that one down, found the parallel protein in humans, and looked for variations that might be responsible for Bilginturan's syndrome. "But we couldn't find any variations that matched the pattern of affected and non-affected family members."

Philipp was thinking constantly about how to obtain specific types of cells from the patients. One thing they'd do while we were in Turkey was to take peripheral blood – from patients' veins – in hopes of obtaining endothelial progenitor cells. "They would form the endothelium of vessels, and that could give us a basis for looking at the hypertension," he said.

Ideally, they agreed, it would be best to get blood from the umbilical cord during the birth of an affected child. There they would find rich troves of stem cells that could be stimulated to differentiate into any type of cell they needed. "We'd have to get it during the birth and have it sent immediately to Germany," Philipp said. "Do you think any of the girls will become pregnant in the next year or two?"

Okan and Sylvia named some of the girls who were about marrying age, and Ali's daughters might be having more children soon. But obtaining umbilical cord cells would be delicate – and difficult – to arrange. And since there was no way to diagnose the condition at birth, they might end up with cells from an unaffected family member.

"There's a three-year-old in the family who will be interesting to look at," Sylvia said.

"It's tough," Fred said. "Hand development usually isn't far enough along at that age to get a clear phenotype. And the hypertension increases directly with age; babies don't have it at any level where you can distinguish them from perfectly healthy kids."

"The family claims they can tell whether a child is affected or not right at birth," Okan said.

"I'm hoping we can get it down to about three years," Fred said, pessimistically.

He was still interested in the fact that in the past, all the affected individuals seemed to have died of hemorrhagic strokes. "There are a lot of other things that go wrong in hypertension," he said. "Usually the walls of the blood vessels are damaged, you'd expect more of them to get arteriosclerosis and die of heart attacks. But of all these people, it's curious that only one – Ali – has had a heart attack. He probably has an additional risk factor, because none of the others get it. They seem to have some sort of natural protection."

Okan was planning to have a look at fats in the patients' blood – cholesterol and other lipids. Some sign of the protective factor might appear there.

On Thursday morning the work began in earnest at Cafer's house. Each patient would rotate through various stations. The first stop was in the living room with Atakan and Sylvia, for an interview to check the pedigree, updating the family tree with any new births and checking the information they had. While they were at it they would capture basic medical information – was each affected person taking medications? Which ones? Had they had other health problems in the meantime?

Then off the person would go to Philipp, between the living room and the kitchen, to get a good image of his or her face, hands and feet, and to take height and weight measurements. Next in line was Fred in the girls' bedroom for blood pressure measurements: lying down on the lower bunk bed, and then sitting. The affected individuals were too short to bump their heads on the upper bunk, but that happened to Fred and some of the rest of us.

In the bedroom of Cafer's mother, Okan would draw blood and then hand each person a white plastic cup for a urine sample. At first it was embarrassing – particularly for the girls, he said, and left it up to one of the women to ask. But after a day or so the sights of the cups traveling back and forth became a common sight.

I couldn't help thinking of the last lab I had worked in, which had a reputation for some classic April Fools day jokes. An urgent e-mail had gone out to the staff on March 31, stating that the health ministry had tightened its rules about work with infectious agents and radioactive materials. Everyone was supposed to leave a clearly labeled urine sample in the personnel department. When the administrators arrived the next morning, they found

dozens of cups, beakers, and other laboratory containers lined up in the hallway in front of their doors, with an interesting assortment of liquids inside.

On the last day the researchers planned to take small biopsies from some of the patients' hips, which involved removing a bit of tissue with a tiny stamp-like device that penetrated a couple of millimeters into the skin after the application of a fast-acting local anesthetic. It's a short procedure, virtually painless, and the only after-effect is that the patients have to wear a Band-aid for a few days.

The house was small, and you seemed to be able to hear everything: the questions from the interviews, the snapping of the shutter and the flash on Philipp's camera, the beeping of the blood pressure machine. People talking, nervous giggles, and occasionally a child crying at the prick of a needle.

Right from the beginning it became clear that things wouldn't necessarily run smoothly. The very first patient that Sylvia and Atakan interviewed claimed that she didn't really have high blood pressure.

"It's because I'm nervous," she said. "I check every day, and it's only high when I get excited."

She wasn't enthusiastic about giving blood, and she hadn't been taking her medications. "She says it made her dizzy," Atakan translated. "And she had some blurred vision, and a tingling feeling in her arms and legs."

She had taken the drugs for a long time, but when these symptoms appeared about five years ago, she stopped.

"There are other drugs she can try, but she *has* to take them," Sylvia said. "Make a note – she has to talk to Okan."

One of the young boys said he didn't have any problems except that when he played with his friends and ran a lot, his legs hurt a little.

The small children chattered constantly, to all of us, even when no one was around to translate. Apparently they didn't believe that we couldn't understand a word they said. They grabbed our fingers and dragged us outside to show us the barn, or a cat, or something that only they seemed to see.

Over the next few days they tried to teach me a few words or phrases in Turkish, but my best attempts to imitate them made them howl with laughter. One of the girls had me repeat a phrase over and over. "What's she trying to say?" I asked Atakan.

He smiled. "She's teaching you to say – well, the literal translation is that you're carrying around about 15 kilos too much baggage." And pointed at my belly.

The father of the three-year-old, who was about 25, told us that he had a steady job in Bursa, the city that lay to the southeast of Istanbul, and was taking his medications regularly. "But for a while I stopped," he said. "I used to go out drinking with my friends." That was a problem, Okan said, because it wasn't good to combine alcohol and the drugs; it left him completely exhausted.

He had been a young boy at the time of the original study. He did have insurance, however, and his doctor had noticed his extremely high blood pressure.

"They gave him a lot of drugs," Okan said. "After trying a lot of different things, they finally 'hammered' his pressure down below 140. Usually it was over 200. They tried too fast, probably because they didn't know about the syndrome and were panicked. Finally his pressure was okay, but he was totally listless. Normally you need to develop the therapy slowly, maybe over half a year. During one period they gave him lots of diuretics and he had to urinate constantly. Right now he isn't taking anything."

The young man told us that the study and the visits of the scientists opened his eyes a bit. "If we hadn't been here," Okan commented, "no one would have thought of taking his blood pressure. It's interesting because we've brought a lot of attention to symptoms that traditionally

haven't been given much attention – nor, in the rest of the world, until a few decades ago."

It was good for the health of all the affected people to have noticed the problems early. On the other hand, it has provoked unusual responses from people outside the family, that there's something "special" – not only in a positive sense. "Some find it good, but others are a bit jealous that our family is getting all this attention from people from abroad," the young man said. "They ask, 'Why aren't they paying any attention to us? Some of us have high blood pressure, too.'"

"Damned if you do," Fred remarked; "damned if you don't."

The second evening, everyone who wasn't working and a various assortment of neighbors and relatives sat in the living room watching a soccer match on television. When Philipp had to weigh someone or take a picture, they leaned to the left or right to get a better view of the screen.

Turkey was playing Argentina. Whenever Turkey scored a goal, gunshots echoed through the hills and valleys.

Talking with some of the women and children from the village gave us a few sharp and poignant insights into sharp cultural differences, and how much life around the family has been changing in recent years. Getting them to talk was another matter. The women, it turned out, were willing to speak freely – once the men had left the room. And the children had a lot to say

One question that interested me was how young people in such a small village met their future husbands and wives. Apparently there existed something like a local "matchmaker"; otherwise, relatives often took the initiative in bringing likely candidates together. The story told by Cafer's wife was perhaps the most typical for many of the families two decades ago.

"We were brought into a house but didn't directly meet," she says. "I didn't really know him at the time. We were in separate rooms, and there was a door with a small window covered by a cloth. I was allowed to briefly lift the cloth and look at him. Then I said whether I thought I could accept him as my husband or not."

She laughed when she says that at first, she wasn't terribly impressed. But somehow they were matched anyway. And after the arrival of three children, and the establishment of a harmonious household, things seem to have turned out fine.

The most dramatic story came from a heavy-set woman with a cheerful demeanor and a firm voice. She told about how his son found and married his current wife, twenty years or so ago.

"My son was dating a woman, but she dropped him and started going out with someone else," she said. "What was wrong with my son? It was bad for his reputation!" So, she said, she got her shotgun, went to the young woman's home, and basically kidnapped her. She took her to her son's place, made them sleep together somehow (the details were sketchy), and then, of course, they had to get married.

"That's horrible!" a friend of the old woman said. She told me quickly, "That doesn't happen anymore."

"You try that now, you get arrested," said another friend.

"Well," said the woman who told the story, "They have four children." This fact was delivered with the authority of evidence showing that once again, things seem to have turned out fine.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At first it is the dramatic things about a truly foreign culture that are the most striking: your utter inability to make yourself understood in any of the languages you know, even in the simplest situations; the calls to prayer rising over the hills every couple of hours; the cow that lives so near the house that Cafer's mother herds one over the terrace to lead it down a path into the gardens. The fact that women's arms are always covered, and their hair so well hidden by scarves that you have no idea whether they are blondes or brunettes.

The girls showed Sylvia and Maj Britt how to put up their hair in the scarves. "No, not like that – this way," Cafer's oldest daughter said. For the rest of the day both of our colleagues went about their business with covered heads.

After a few days, the smaller bits of strangeness become obvious. For me, the floral patterns on every fabric and surface were striking. It gave the rooms a busy feeling, but there was something missing: there was almost no artwork on the walls, or photographs of the children, or calendars of foreign landscapes. Most houses had steps that seemed built into the wall and ran perpendicular alongside the house, rather than stretching outward and down from the front door. And always a huge collection of shoes at the top before the proper entrance.

One evening we came down and rummaged through the shoes until everyone had the right pair – except for me. My left shoe was gone, and no matter how many times I looked through the collection, it was nowhere to be found.

At first I thought one of the children had hidden it as a joke, but then the entire family got involved, looking for the shoe.

"Maybe a cat took it," one of the younger children said.

"Not a cat," her brother said, scornfully. "If it was a cat, she wouldn't have dragged it very far. A dog."

"Maybe my shoe smelled really sexy to a dog," I agreed.

Atakan thought this was hilarious, and for months afterwards he reminded me that dogs thought my shoes smelled sexy.

Well, there was nothing to be done – the shoe had vanished. So Cafer's wife dug around until she found the only pair they could loan me that fit: a pair of plastic purple sandals. They were tight at the toes, but at least I could walk in them. After we left we had to do some shopping, and I walked through the market with my plastic purple shoes. Self-consciously, of course, but nobody seemed to notice. The shoes probably didn't seem any stranger than the rest of my appearance. I wore them to the car, to the hotel, and to my room. I didn't put them in front of the door. Maybe I should have; maybe some animal would have stolen one and I wouldn't have to wear them anymore.

The next day when we arrived at Cafer's house, there was my left shoe, standing beside its partner. At dawn the grandmother had sent all the children into the hills looking for it. One of them had been successful, and the next day I brought along some chocolate as a reward.

The left shoe had a small bite taken out of the heel.

"Very sexy to a dog," Atakan said, and laughed.

Retreating to one of the bedrooms, Cafer's children and one of their cousins also became eager informants about their lives, which mostly revolved around their friends at school and life in the village. Okan had told me that the Turkish government has taken the situation of its citizens into account in planning aspects of their lives such as the length of time they are required to go to school and the rhythm of the academic year. In rural areas, at least a few years ago, the minimum requirement for attending school was only six years. This meant that at

the age of 12, many children stopped attending and went to work on the family farms or take on other jobs. In the cities, he said, it was nine years. And in the summer there were long breaks of three or four months so that the kids could participate in the harvests.

The eyes of Cafer's youngest daughter Emine flashed as she spoke; she gestured quickly, as if eager to reach out, grab life, and give it a good shake. "My life is so interesting I could write a whole book about it," she said. She went to school in the nearest town on the coast, and her favorite subjects were math and English. She liked to read the novels of Charles Dickens – her favorite book was *David Copperfield* – and Charlotte Brontë.

But her classroom was so small that it was uncomfortable. "It took a long time to get used to school," Emine said. "The teachers and the staff are very strict with the kids."To ease the tension, she said, they played small practical jokes on each other. Mostly the classics: attaching a sign to somebody's back that said, "I'm dumb," or "Kick me."

Most of the other children came from the towns; they all had cell phones and were always listening to music on them. "They don't play together or do much together," she said sadly. "I was born here, opened my eyes for the first time here, but I always wanted to see what it was like in the cities," she said. "Now that I've seen several towns, I think we live in the most beautiful place there is."

One of the earliest memories of her older sister Nazlan was being lost somewhere on the family farm. And once, when she was very small, she envied the fact that their older brother had money. She wanted to know what it was like to walk around with money in her pocket, so she "borrowed" some. And then went out to play, and lost it.

Nazlan remembered another time when she rang the bell downstairs. Her brother was home, but he didn't answer the door, so she kept ringing it. "And then the little button got stuck and it rang a long time," she said.

Like children everywhere, the siblings sometimes got into fights. They take things from each other – and, yes, have hit each other from time to time. "Most of our fights are about clothes," the older daughter said.

"Why do you wear my clothes?" Emine said.

"Why do you wear mine?" said Nazlan, and they laughed.

"Do you like to sing?" I asked them.

"I do," said Emine, and when I asked, she sang a song for us, with her brother and sister sitting there, without any self-consciousness. My own children would have died of embarrassment before singing in front of each other or a complete stranger.

"I know that song," Atakan said. "It's a famous Turkish pop group with three women singers. One of them just quit."

"So now there's an opening for you in the group," Ercan told his sister, and Emine laughed.

He had been four or five years old during the first visit from Fred's team, an event so unusual that Ercan could still remember it. "He didn't know what we were doing, but he can remember the gifts we brought, and remembers that he was a little afraid of what we wanted," Okan said. "He didn't like being stuck with a needle, but later we were 'known quantities' and he was always excited when we came."

Now Ercan had a lot to say. "I'm the first-born," he said, with pride and a bit of irony.

"Big man," the older sister scoffed.

"Macho," he laughed, thumping himself on his chest. He talked about his father. "A person's father is important, is number one in the family. It's not like in Europe or America; I hear sometimes they throw you out of the house when you turn 18." It's a fact that seemed to have been weighing on his mind; Ercan had just turned 18 himself. "If I need money or something, he gives it to me."

He liked the fact that he stayed in a boarding school in town during the week and usually only came home on the weekends. "I like seeing all of these new things," he said. "But it isn't always great. In the village it's better; you can yell, play, run around, and make noise – and nobody cares. In town, there are more rules: they have to be careful of strangers; they have to be quiet or they'll bother somebody. It isn't like that here; there's nothing dangerous here."

But he enjoyed being away from home, because his parents never hesitated to interject themselves in his "business" or tell him what to do. At school some of the teachers were strict, but mostly the older ones. "The younger ones are nicer; you can really talk to them, and almost be friends with them."

He was thinking about going to the university; he was interested in the social sciences. "I like philosophy the most. I've read Aristotle, Socrates, Plato… If you study these things, you get to look deeper into life, and ask a lot of questions about things."

His role model, he said, was an old man who lived in a village a little farther way. "He's 70 years old and he's an example for everybody. He's had a lot of problems in his life, but he never stopped learning or fell into a depression or anything. If you ask him something, he always has an answer. He lives well, the way a person should live."

I asked the children if they wanted to ask Atakan or me any questions, and they thought about it for a while. "Why don't you shave off your beard?" Emine asked, and they laughed. I had to wait until Atakan translated to join in on the fun.

"When I met my wife I had a beard, and she won't let me shave it off," I said. "She says she'll leave me if I shave it off. Plus I'm too lazy to shave every morning."

"You'd look a lot younger without a beard," Emine said shyly.

In a group of four children, I had already come across a philosopher and an avid reader, and Mehmet's daughter Tülay was about to provide an even greater surprise. At 23, she was the oldest of the group. Later Sylvia told us she thought the young woman had terribly sad eyes.

Among the women, she was perhaps the only one we met who had finished school, then gone to a college where she had studied religion for four years. There she enjoyed the lively, interesting debates that centered mostly, but not exclusively, on theological topics. Now that period was over, and she admitted to being a bit bored. "Most of my friends have gotten married by now," she said. "Then they usually move away. Not too far – mostly to neighboring villages – but we don't see each other very often."

They still got together and discuss the changes in their lives, but she felt a bit lonely. Sometimes, she said, she wrote about her feelings in poems.

"I know a person's poetry is often very personal," I told her carefully, "but I'd love to hear one."

Tülay promised to bring one along the next day. And when we arrived in the morning, I saw her coming up the path with a big purple book tucked under her arm. Her cousin hadn't been too shy to sing for us, and this young woman seemed more intrigued than self conscious that someone might be interested in her poetry. It took us a few hours to find time to sit down with Atakan, but finally, late in the afternoon, we got to hear the poem. And you will, too, at the close of this chapter.

During one of our many drives, Okan told me about a few of the ways larger issues had reared their heads during his year with the family. "The Turkish government and the people are all aware of projects where people appear just long enough to get data for their publications and then leave," he said. "That has had a very negative impact on people's feelings about science, and it goes beyond

Russ Hodge

that," he said. "It always leaves a bad taste that smacks of misusing people. It's particularly sensitive when representatives of a 'civilized' land come into a 'less civilized' country or region to do some sort of fancy, high-tech procedures. Particularly among people who haven't been directly involved with us, they have made comments to family members like, 'They're just using you,' and we've been highly aware of the fact that our visits implicate us, that we have to take responsibility. If you do that, you not only save lives, but you enjoy the personal contacts you make – it gives you friends for life!"

Things don't always work out so well, Fred pointed out, and the problem doesn't always lie with the physicians. He told us about a project involving a large family in Syria with a serious metabolic disease. "They can't produce a protein called an LDL receptor, which is crucial in the processing of cholesterol," he said. "They have tremendously high levels of cholesterol, which collects under the skin, at characteristic locations like the elbows, the Achilles tendons, etcetera. We were looking at a family in Damascus and ended up traveling all across Syria to find them. We found people in their twenties with really bad atherosclerosis, and bad aortas."

The situation was particularly frustrating, he said, because there was no real cure. "You might be able to carry out some sort of dialysis where you clear the lipids from their blood, but it would be temporary, and the problem would come right back the next day. It's probably better than nothing, but Syria doesn't have the resources to do it anyway." The subjects were terribly isolated, he said, and not very friendly to people carrying American passports, but he made the effort. "It was an interesting experience. I probably should have checked in with the State Department, but I didn't bother." He rolled his eyes. "Yet another legal and ethical problem with trying to do basic medicine across international boundaries. Of course there's a sense to it, although a genetic disease doesn't care about your nationality."

Okan recounted another case that had come up during his year in Turkey. "One of my patients was trying to get pregnant, and it's not a very good idea to have an expecting mother involved in a double-blind drug study. You can't tell the physician what medications she's receiving because you don't know yourself. So I discussed it with her gynecologist, and we decided to discontinue the treatments. It was the right thing to do; it would have been a real case of 'abusing' a patient."

"So these things have come up from time to time, but now, fifteen years later, we're still here," Fred said. "There have been some difficult decisions, but thank goodness we seem to have made the right ones."

"The contact became very intensive, and the children in particular have grown up the whole time knowing us and being involved in the project," Okan said. "I think all of our patients are now aware that this prejudice against foreign researchers isn't always justified. So what we have accomplished is not only a good example of research between cultures, but research between particular types of cultures. It's our responsibility to respect the personalities and wishes of the family, and to put those things first when dealing with these people. It's extremely important. It's not a matter of law, but a matter of human principle."

One thing I had noticed during the week was an almost complete absence of art in the lives of the villagers. This may have been a false impression due to a sample that was far too limited; it may have had something to do with their faith, or simply the fact that we were visiting a very hard-working group of people who were confronting much more important issues in their lives.

Perhaps the feelings and sensibilities that Westerners find in art were kept private here; the way the length and color of a woman's hair were considered a privileged aesthetic to be appreciated only within a family.


The
DOCTOR
is
IN

But I had noticed the almost complete lack of paintings or photographs on the walls; ornamentation seemed mostly restricted to patterns on the fabrics. At one point I realized that the children seemed never to have seen someone draw a sketch, or perform a magic trick – one afternoon they kept bringing me pens and paper to whip off a version of Snoopy on his doghouse, or Lucy snatching away a football and sending Charlie Brown flying through the air, only to land on his back with a "whump!"

Sometimes the constraints of a particular style permit the emergence of a beauty that is subtle to the untrained eye, but very deep; sometimes freedom of thought can emerge in a spectacular fashion from discussions that occur within a strict framework of thought. I remembered what a Jewish friend who was studying theology had told me about a discussion between two rabbis on the intricacies of Talmudic law – "It's like watching two grand masters play chess," he had said.

And weren't the scientists doing the same thing? The strict rational framework of molecular biology – based on the laws of chemistry, and physics, and the enormous vision of evolution – permitted amazing flights of creativity.

Still, I kept looking for a village artist or storyteller. I didn't meet one of those, but I finally had an encounter with the musical culture. The scientists knew I played an instrument called the *viola da gamba*, a Baroque instrument played between the knees like a cello, with a bow, six or seven strings, and frets. Similar instruments appear in most folk music traditions around the Mediterranean and throughout Europe, and I wondered if there wasn't something similar in the Black Sea region.

It turned out there was – a small, three-stringed instrument called the *kemençe*. Okan and Atakan had made queries and found out that there was an instrument-maker with a shop in a nearby town. So on Saturday we stole a couple of hours and made the trip to his shop.

Kemençes, Arabic lutes, and other instruments hung from the ceiling and walls. The bowed instrument was a bit different than the others I had played, with thin metal strings that bit into your fingers, and the bow was a crude stick that you had to practically stick your fist through to tighten the horsehair strands that came in contact with the strings. But the technique for making sounds was virtually identical.

After a bit of advice on the tuning system from the old man who ran the shop, I scraped out a tune. He was delighted.

"How much for the instrument?" I asked. He bit his lip and named a ridiculously low price. There were dozens around the shop, and I tried out a few until I found one that produced an even, less raspy sound.

Fred floated me a loan, and I left the shop as the proud owner of a kemençe.

That afternoon the physicians set up a consultation booth to consult with the affected family members about plans for their medications. Thinking of Lucy's psychiatric booth in Charles Schultz's "Peanuts" cartoons, I made a sign: "The Doctor is IN." Out came the big black suitcases with the hypertension pharmacopeia we had, ah, "escorted" into the country at the beginning of the week.

As Fred and Okan talked to the family members – as well as an assortment of neighbors who appeared with various complaints besides high blood pressure – I got out the kemençe and played an English folk tune. Children seemed to appear out of nowhere and gathered around.

"You're playing it like a *violin*," one of them frowned. No, I wasn't holding it under my chin, but I had no idea what sort of music they played on the instrument.

Within an hour they had summoned the husband of a distant relative; many years ago he had played the kemençe in a group. He limped up to our small doctor's station and played a song. It was hard to follow the melody,

which was buried under fluid trills, and just when you thought you'd figured out the rhythm, it jumped to some other system. But it was clear that you were supposed to play two strings at the same time, fingering both the same way, and after a few minutes I could perform a passable imitation.

He grinned at me, exposing gaps between his front teeth, and clapped me on the shoulder. The children dashed off to get their parents. An alien creature had appeared in their midst. He couldn't speak a single word of Turkish, but had managed to communicate in a language that was somehow much more fundamental, one that can sometimes jump across barriers that lie much closer to the heart.

On Friday we had taken time off to go to the bazaar in a large town on the coast. Mehmet parked the van beside a crumbling building that seemed to hang from a high, ancient city wall. We climbed out and followed a walkway along the pier, where an assortment of colorful fishing boats was tied up, amidst huge snarls of nets. Two fishermen were untangling one of them and repairing tears.

The market made a vast circle around the old part of town on the waterfront. So many vendors were simultaneously advertising their wares in shrill voices that I doubted even their customers could understand them. The air was pungent with the odors of fish, freshly baked bread, and huge cakes of cheese, as well as the occasional, strange smell of unfamiliar chemicals.

We passed stands selling ancient farm implements, wooden bowls and spoons, fruits and vegetables, bolts of cloth in every color and every conceivable pattern. A mass of eels squirmed in a crate with just a few centimeters of water in it. Chickpeas, types of beans I had never seen before, tomatoes, gourds, dates, pomegranates and melons, flowers, baked goods dripping with honey, metal pots. And two brightly colored buckets of powder, open, which turned out to be rat poison. And, most incongruously, a stand where women in long dresses and scarves critically examined silk lingerie.

It was stunning and noisy, with hundreds of people bustling about, carrying off their purchases in plastic bags.

As we wandered along what seemed like miles of stands, Cafer hurried up with his cell phone. There was a problem. "The state militia is looking for us". Okan found Fred and Mehmet and had a hurried conference. Apparently the doctor we had met at the hospital on Wednesday had made a call to the Ministry of Health. It seemed he had informed them that there was a group of foreigners in the region, carrying out some sort of medical research project, and he wasn't sure that we had the proper authorizations.

The ministry had then called the mayor of the village, the man we'd met during our first evening in Turkey. He was fully informed, of course, and told them that everything was in order; no one was being asked to do anything against their will, or anything unethical. But the call had alerted the Governor's office, and they sent a request to the military police to investigate.

"It's better that we go to them than they come looking for us," Okan said. A quick decision was made: the mayor, Fred, Okan, Sylvia, Cafer, and Mehmet would find the Gendarmerie and go talk to them. They would catch up with the rest of us later.

They were gone for about two hours. Atakan, Philipp, Maj Britt and I stayed in the market, but it certainly put an edge on a morning that was supposed to be devoted to shopping. At least there was one success on that front. We had been keeping our eyes out for a nice bottle of red wine for Fred; he had found most of the offerings in the hotel undrinkable. On a corner we found a dubious little shop that sold cigarettes, tea, and wine. Some of

the bottles appeared to have been "refilled", but we found a bottle of red Bordeaux that didn't seem to have been tampered with. Now we only had to wait for the police to release our friends to enjoy it.

They were having a better time of it than the things we had imagined, some of which were pretty bad. The mayor led the way to the Gendarmerie, which was located across the road from the wall in a new building. He held the door as they entered, and the group was ushered into a small office with a simple wooden desk, where the "Chief" and another senior official were doing paperwork. Also present were two officers with machine guns. They set up enough chairs to accommodate the group and the Chief ordered tea. The second official moved to a chair near the wall, where he sat the whole time without saying a word.

When it was served, the mayor made a short statement about what Fred and his team had been up to. "This project has been going on for a long time," he said. "They've been coming for many years, always with permission, and there has never been a problem. They have become almost friends of the family."

The Chief asked a few questions. The biggest problem seemed to be that no one had the slightest information about what was going on, but strange rumors were floating around. As things turned out, the group's credit was high going in. The mayor was well known and highly respected at the Gendarmerie.

Then Okan began to talk. "He spoke for about half an hour," Sylvia said. "We couldn't understand him, but it was obvious that he was giving a big, flowery speech."

Okan introduced himself as a physician of Turkish descent who had spent his whole life in Germany; his father had lived there for 47 years. "I'm a doctor, and in Germany, you are assigned to another physician who's your 'doctor father,'" he said. "In my case that's Friedrich Luft, who's sitting here. He's very famous in Germany, at a prestigious institute, and we've been pursuing this project with another very famous physician in Ankara."

He talked for a while about the family's health problem, and explained that Nihat Bilginturan had looked after them for a long time, but now he was an old man. "We've always worked with official support and have done things by the book, and we tried to do so this time as well." Okan recounted their efforts to obtain authorizations, listed the officials who had contacted, and explained that there had never been an official response.

All the while the Chief took copious notes and interrupted from time to time with a question. Although he wanted concrete details, the atmosphere, Sylvia said later, was much more comfortable than our session with the hospital administrator at the beginning of the trip.

"You can look us up in the Internet," Okan suggested. "We named the syndrome after Doctor Bilginturan, and now it's known all over the world."

That would be difficult, the Chief said. Their computer had broken down. But he took more notes. Everyone sipped tea.

"Well, anyone who is spreading rumors just doesn't have the necessary information," Okan said.

"You say you're looking for a gene," the Chief said. "Have you found it yet?"

No, Okan replied, but the group was still working on it. Then he had a sudden inspiration.

"What we'd really like to do," he said, "is find a local person who can take care of this family, who have really grown in our hearts, especially to help them financially with obtaining medical care and the proper medications. We've tried to do this several times, but you know… Doctors here have other things on their minds and other interests."

Okan Toka and Cafer

"Maybe we can help," the Chief said suddenly. A new law had just been passed, giving the Governor the authority to appoint a physician on a special assignment to take care of a group. "It's a new law," he said, "So the details are just being worked out."

"It would be terribly important to find out how to do this," Okan said.

"The model is based on the 'family doctor,'" the Chief said. "If the family can't afford it, the government will assume all the costs. The thing to do is to arrange a meeting with the Governor."

"Can we do that right away?"

The Chief told one of his men to put through the call. Unfortunately, the Governor was gone for the day. But there was a clear way to proceed. The mayor and Cafer could contact the Governor's office and make an appointment. They could explain their case and ask for help.

"As far as the local authorities are concerned, the situation is resolved," Okan said when they rejoined us later. "Not only that, the family's situation looks much better than it ever has before. Finding a local physician who is dedicated to the case would be an ideal solution for the long-term."

And the group probably wouldn't have heard about the new program, he added, without the rumors that had somehow reached the Gendarmerie. Maybe by putting up a fuss, the hospital administrator we had met on the first day had inadvertently ensured the future health of a family in whom he otherwise expressed no interest at all.

On Saturday, Okan and Philipp had their hands full with taking the small biopsies from patients' skin, to obtain fibroblasts. They also drew blood, which had to be done as late as possible in the trip, since the endothelial progenitor cells they hoped to find there would not survive very long in the sample tubes. The family formed a long line outside the door of the grandmother's bedroom.

Okan, the MD, administered a local anesthetic and applied the small "punch" to the patients' arms. Philipp removed the skin from the punch, each time sterilizing the scissors and forceps he needed for this procedure. Sample tubes had been prepared with numbered stickers – the patients names couldn't be used, because their identities had to be protected during the process of analysis. Philipp matched the numbers again and again – a single mistake could invalidate all the results.

As they waited in line for their turn, some of the girls giggled nervously and made jokes. Those who emerged from the room after the procedure told their friends it hadn't been a big deal. "One girl who hadn't been planned into the schedule even volunteered," Philipp said. "It seemed to be a sort of test of courage, and she did well."

One girl fainted – to the delight of her friends, when they found out. "But we lay her down on the bed and after a few minutes, her face was rosy and she laughed about it," Philipp said.

For Okan and Philipp it had been the most stressful day, but by evening they had taken biopsies and blood from 35 patients. "We were really ready for Turkish mocha, beer, and raki!"

The last morning before departure, Mehmet raced the scientists down to the clinic to pick up the samples that had been stored there. Others had been kept in the freezer in the hotel kitchen, along with ice packs, and everything had to be prepared for the flight back. The materials had to be reorganized and repacked,

"It was stressful, and it made us very late getting to the airport. But we made it. Now our only worries were getting the stuff back into Germany," Philipp said.

Cafer always seemed to be everywhere, somehow managing to take care of any small needs that arose, yet slipping off several times a day to make the call to prayers from his mosque. One of his tasks was organizing trip to Mecca that several members of the community would be taking very soon, a pilgrimage that most Muslims regard as a sacred obligation to perform at least once during their lives. Somehow at the same time he was carrying out his normal duties as Hoca, including the delivery of an hour-long sermon and leading prayers on Friday. Then there were matters concerning the farm – once I saw him outfitted from head to foot in white, beekeeper's garb with the mesh hat, tending the family hives.

"What did he talk about in the sermon?"

"Some days have special themes. Today the topic was the establishment of the state, so he spoke about democracy. Democracy is an important theme in Islam; in general, social themes overall are important. So he discussed the establishment of the state – which, since the establishment of the modern constitution by Ataturk, has been secular. He talked about how people should be true to their country and respect democratic principles.

"It's a bit different from most Christian traditions, where you have a church calendar that's established during the year. Sometimes like today there are set themes to be discussed, but as Hoca he's deeply involved in the details of daily life, and so if there isn't anything particular going on he can choose what he wants to talk about. Often these are quite practical matters – such as the participation in our study."

A recent example had been an outbreak of the swine flu – which had lain Okan's brother low in the United States, preventing Hakan from making this trip with us. To cope with what was widely perceived as an oncoming crisis, the ministry of health had held a seminar for religious leaders, in which physicians and other experts provided instructions to Cafer and his peers. "They advised the religious leaders on health-related issues they should share with their congregations," Okan said. "Things like, 'Tell them to avoid shaking hands.'"

So Cafer's role is a fascinating one, in social terms. He is the link between the long, historic tradition of Islam and the practical problems of his community; namely, the link between religious doctrine and modern life.

But the major weight he carries is one faced by the rest of the world, and particularly villages like his own: the way small farming villages that have barely changed since the Middle Ages are being swept up in a highly technological world. The modern industrial countries of the West have had more than a century to go from horse-drawn plows to the Internet. This almost ridiculously short span of time causes considerable problems for a lot of older people in our society.

Well, in Karamat that process has been exponentially accelerated and compressed to a span of time of just three or four decades; Cafer had experienced it all between adolescence and adulthood. When he was nine years old, his father Kemal had ridden down the hill to pick up Nihat Bilginturan on a mule. Now he was not yet fifty years old, and his two daughters were sitting in the living room surfing the Internet on a laptop.

In this context it is easy to see how countries such as Turkey – with so many rural villages, many even more isolated than this one – face vast problems as their society attempts to develop in a peaceful and harmonious way. It is little wonder that they are defensive in the face of foreigners who arrive with their own agendas and often intentions that are exploitive rather than honorable. What is stunning and wonderful is the fact that they would greet any of us with such warmth and open arms.

I finally got the chance to talk to him on our last day, during our drive to the airport in Trabzon. It quickly be-

came clear that Cafer's awareness of the problems and the overall situation reaches far beyond the situation of his particular village.

He spoke of the immense plurality of Turkey, which has deep roots in history, geography, and differences in culture. The western region, where Istanbul lies, has closely followed European developments and adapted to them, mostly through a process of education. The theme of education is a central for Cafer, who believes that it represents the only chance for his family, his village, and his country to develop in a healthy way. That's difficult because throughout the rest of the country, the level of education is much lower. In the Asian regions of the East, and particularly in the Southeast, this has posed an enormous challenge.

"If your father hadn't moved to Germany," he told Okan, "you never would have become a doctor or had the opportunities that have been given to you. Here on the Black Sea most children received only a grade school education."

In his own village, there was a tiny schoolhouse where children were only given a very rudimentary, basic education that ended at about the age 11. It was only in 1970 that they had managed to get some of the kids into a sort of middle school and keep them there for a total of nine years. Achieving that required most of the villages to send their children to schools in the towns on the coast.

But even then, Cafer said, very few of the young people "got out." Even today, only about 30 percent of the population progressed to the level of some sort of modern university, and there are still huge regions of the country where that is not the case.

"Many of our problems come from this," he said. "Most villages don't provide enough schooling, and the regions haven't adjusted at the same rate. The great differences in cultures and education create tremendous problems for the country's economic and social infrastructures. And it is very hard for the politicians to cope."

In the southeast, for example, local rulers, individuals with centralized powers that seemed limitless, ruled regions. They made decisions regarding who should marry whom, who could get an education, and overall, what was to be considered right and wrong. "This makes it into a self-perpetuating system," he said. "It just ensures that the problem will continue for a long time to come."

It was disappointing, he said, that such types of problems tended to attract the most attention from the international media. And one of the most unfortunate problems, he said, was that the world had developed a fully inaccurate view of Islam.

"Religious freedom is firmly anchored in the Qur'an," he said. "A Christian can marry a Muslim, for example, without having to convert to the Islamic faith. A Hoca can marry two people of different faiths, and the partner may keep his or her religion without being asked or forced to adopt a new one. This can only be done if the partner decides freely to become a Muslim."

He was aware of a recent controversy that had arisen in Germany, France, and several other countries about women's clothing. "The Qur'an states only that a woman should keep herself 'covered'," he said. "This does not in any way imply that they must be completely covered, or that her face should be hidden. Instead, it means that people should be appropriately dressed according to the society in which they live. My own daughters, for example, wear a head covering, but no one forces them to do so. They are choosing to dress according to the local custom, and that will surely change. In the cities, for example, women wear makeup and have uncovered hair, and that is the appropriate dress for a Muslim woman who lives there. None of this is proscribed."

Cafer also felt the need to discuss the fanatical terrorist movements that have so strongly influenced the perception of Islam over the past decade. "We are absolutely peaceful people," he said. "To take the life of a single per-

K.Y.

Muhtaç olduğum gönül çok vaktlerde
Bırakıp gitmiş beni başka diyarlara
Anlamamış ona ne kadar muhtaç olduğumu hala
Bırakıp gitmiş beni başka diyarlara

Şiirler yazmış sever peşinden
Mısralara dökmüş derdini caresizlikten
Ne olur dön demiş bırakma beni çaresiz
Oysa sevdiği çoktan gitmiş o hala habersiz

Gözler yüze muhtaç kalmış hep birini aramış
Gönlü sevgi ateşiyle yanar yanarda coşarmış
Hala dön dermiş bırakma beni çaresiz
Ümitsiz bir sevgi uğruna ümit bağlarmış

MALESEF GEÇERSİZ...

son is the equivalent of taking the life of all humanity. Taking a life is the greatest sin that a person can commit. The people who do these things are not Muslims. They are acting for political reasons, and they particularly come from regions that have suffered from great underdevelopment and a lack of education. The people who live there may say that they are acting out of religious motives, but these are empty words. They are only repeating what a disturbed person has told them, and they do not have the education to understand what they are truly doing.

"Islam places a great value on education," he repeated, "and generally on education and progress, which includes scientific progress." During the trip we had witnessed the practical application of this philosophy within his own family and community. He has ensured that his own son and daughters receive as much education as they desire. "This is our future," he said. "They are our future."

I never believed that there was anything fundamentally different about the lives, dreams, or aspirations of our hosts or their children, and the best proof came from our young poetess. What she shared with us concerned a lost love – surely a real person – and I will never forget the courage she displayed in revealing her most intimate thoughts to two middle-aged men from a foreign land whom she had known for barely two days.

K. Y.

My Love, whom I need, is so far away
Left me, left for another place
With no sense of my need, even now
Left me, left for another place

Poems written in the wake of my Love
Sorrow put to words, in place of this hopelessness
Come back, come back and don't leave me helpless
But my Love is so far away, with no idea
How I long for a smile, have always sought the One
How a heart burns for love and catches fire
Come back, come back and don't leave me helpless
Hoping and ever waiting for an echo of my love
That never comes.....

Atakan translated roughly; she read it again. For a moment we were left speechless. I had no idea whether she had any training, had ever met a teacher who helped her craft the language of her family and her people into the vast, minimal art of poetry. But even with no comprehension of her words, the rhythm of urgency and loss came through. The most stunning thing was that she had made the effort at all to use language to cope with her deepest feelings, and was willing to share it with us.

Later Atakan translated the poem into German, always an impossible task, and I translated his version into English, a process in which everything that this amazing young poetess cared about was probably lost. For those who read Turkish, her own words appear on the facing page, in her own script.

It has been three years now since we met these children, and I constantly wonder what has become of them. Whatever happens in the aftermath of this book, I vow to myself that I will find out; I will find out. I truly hope that Cafer's son has started along a path to becoming a philosopher, and will one day be just like the 70-year-old man that he so admired. And that Cafer's youngest daughter continues to have the laughter in her flashing eyes. And that a young poetess has discovered a new love, or recovered the one she lost. But most of all – and I know that this is a bit selfish – I hope they all discover that language is both a consolation for love and a key to it, and a doorway to a much larger world in which science and art and literature can profoundly change our lives and those of many others.

20 All endings are beginnings

Arriving at Tegel airport on Sunday evening, we didn't have any suitcases of drugs to transport into Germany, but there were biological samples that could have caused a problem. "I take full responsibility for everything," Fred assured the customs officers. Had the material been confiscated, there would have been no chance to obtain stem cells or other types that the group needed.

As things turned out, the officials weren't interested in the blood or biopsies, but the sophisticated blood pressure measurement devices attracted their attention. They were the most precise machines available, borrowed from an intensive care ward. "Were these bought in Germany?" an officer asked skeptically. The machines had been, of course, and Sylvia said she could send a report attesting that they had been provided by a German laboratory.

It had been a stimulating trip, and an exhausting one, but for the scientists, a key phase of the project was just beginning. Blood samples had to be dealt with – extracting DNA, of course, but also fishing for new types of cells. Sylvia, Philipp, Yvette, and Eireen Bartels-Klein spent the evening of the return in the lab getting everything stowed away and preparing for the next round of experiments.

In the blood samples, the group hoped to find progenitor cells which develop into endothelial cells lining the blood vessels. "We hoped that in these cells, we could investigate a tissue-specific use of genes," Philipp says, "in a body system that is very likely involved in hypertension." If the progenitors could be isolated from patients' blood, they could be cultured in the lab, and they might reveal differences in the use of genes in family members affected by Bilginturan's syndrome.

Capturing the cells was fairly straightforward if you could start with the blood of a newborn; Yvette had practiced the method using blood from umbilical cords, provided by the HELIOS clinic across the street from the campus. There hadn't been any newborns in the Turkish family, but it was sometimes possible to obtain the cells from *peripheral blood* – from veins, the type used in most medical tests.

The scientists had taken along tubes containing a special medium which would help these specific cells to grow. So for several hours after the group returned, Yvette helped Philipp transfer blood from the sample tubes into cell culture dishes. Within 30 hours of their extraction, Yvette had "put them to bed" in cell cultures in the lab. Now the group simply had to wait two or three weeks for the cells to grow, and then they began scanning the dishes for signs that they had obtained endothelial progenitors.

When Philipp told me about this later, I thought of the strange rhythm that science imposes on its practitioners. Short bursts of intense activity often culminate in achingly long periods of waiting. I thought of the months and years that Atakan and Herbert Schuster had spent so long ago, with the deadening routine of coming in every day to prepare probes, load the PCR machines and the sequencers, and then to start all over again the next morning. I thought of the years that Sylvia and Thomas Wienker had spent digging through the results in search of the locus of the genetic defect. All in preparation for one result, which came as they inspected one chromosome. And then how they'd had to begin all over again to narrow the region down.

Now, inspections of culture after culture revealed none of the cells. "They would have been quite useful," Philipp said. "But maybe we were going to have to settle for fibroblasts again, obtained from the biopsies."

Then one blood sample, obtained from an eleven-year-old boy affected by the syndrome, seemed to show promising results. But under the microscope the cells looked a bit strange. Philipp thought they might be looking at a different type of cell. "A friend of mine from Tübingen named Martin Vaegler had just done his PhD thesis on *mesenchymal stem cells* – the forerunners of cells that form bone, cartilage, and the smooth muscle that lined blood vessels. In rare cases you can find those cells in blood as well."

If that's what the group had found, it would be a great coup – "pure gold," Philipp said. "If that's what we had, we might be able to obtain cell types involved not only in the formation of the family's short fingers, but also in blood vessels. Those might yield clues about hypertension as well."

Philipp took photographs of the cells and quickly sent them off to Martin. Then he spent hours on the phone with his friend, finding out what would be needed to grow mesenchymal cells. He drove to the blood bank at the Charité to obtain human plasma and expensive concentrates of *thrombocytes*, or *platelets*, which release proteins called growth factors that stimulate cell development.

"When we changed the cell growth media, they did fine," Philipp says, "giving us mesenchymal stem cells from an affected family member. It was a great finding. It would allow us to compare the offspring of those cells to their counterparts from people without Bilginturan's syndrome."

Philipp says he owes virtually everything he knows about the conditions needed to culture mesenchymal stem cells – and the types that can be derived from them – to Martin. "He also sent cells from healthy people of different ages to give us controls. Over the last two years, we've learned to characterize and differentiate the stem cells. As a result, we now have chondrocytes and smooth muscle cells from a patient affected by Bilginturan's syndrome."

So far, the only evidence for an inversion in a region of DNA in chromosome 12 in the Turkish family had come from the FISH experiments. Fluorescent markers of different colors had clearly shown that the order of the DNA sequence had become scrambled. But even though the team was confident about the finding and had published the results, Sylvia wanted an iron-clad case.

Molecular biologists were often skeptical about evidence that relied solely on images. "Nobody, including our group, would ever really be satisfied if we didn't have a second type of evidence to support the observation," Sylvia says.

And she wanted to find the breakpoints – the edges of the region that had been flipped. It was the same problem that had confronted Philipp with the brachydactyly family he had studied in his thesis. The closer the group could get to those exact positions, the more they would know about what had gone wrong in the family's DNA.

Once again Atakan and the other members of the lab tried to find the edges of the sequence using a method called *Southern blotting*. The technique is based on electrophoresis: if molecules are placed on a gel made of particular substances, and then an electric field is applied to the gel, they migrate at different rates based on their sizes. The process is used to distinguish DNA, RNA, or proteins that have even slight differences in size.

"But even when such experiments were run hundreds of times, we couldn't find a consistent, significant difference that revealed the breakpoints," Sylvia says. "So we decided to try something else."

Over the past decade, methods of DNA sequencing had become so fast and automated that teams were starting to do *deep* sequencing. The "depth" refers to the number of times the sequencer examines each letter of the DNA code. Fifteen years ago, in the midst of the Human Genome Project, each sequence was examined just a few times. Even though the process is very reliable, this meant that mistakes crept in. And it was difficult to tell the difference between errors and the normal variation found between individuals.

Most of those differences are inherited, or acquired during the recombination of chromosomes that occurs during the formation of egg and sperm cells, but a study in 2011 suggested that each individual human being is likely to have experienced 60 or so mutations during the process of copying DNA to create our genomes.

Deep sequencing could be used to examine the same bit of code dozens of times, so Sylvia and the group decided to ask the company Complete Genomics to carry out the procedure with three affected members of the Turkish family and one who was not affected. "Based on the pattern of inheritance of the syndrome, we hoped to be able to distinguish individual variations from those that were common in all the affected people," she says. "But that meant going through about a terabyte of data from every single person."

The results were prepared in tables that had millions of rows that had to be compared. The group threw out everything that wasn't located in the linkage region on chromosome 12 and began the arduous task of comparing every difference between the affected and nonaffected individuals.

"We're not experts in statistics and bioinformatics," Sylvia says, "so we converted the information into Excel tables and inspected them mainly by eye."

The result was the discovery of a couple of changes in single letters of the sequence, even within a gene. Perhaps – after all – a tiny variation in a gene was contributing to the syndrome. The group ordered sequences for members of the other families as well.

Philipp had finished his dissertation, but his project with the German families who had brachydactyly without hypertension was still moving forward. Now he was investigating the family with brachydactyly that Sigrid Tinschert had recruited in Dresden. Philipp began the same type of analysis he had performed on DNA from the first subjects.

Once again, he ruled out the possibility that the family's brachydactyly was due to a mutation in the main genes responsible for the formation of limbs and fingers. Again, instead, he found that a translocation of a DNA sequence had occurred. The new breakpoint had also occurred near the PTHLH gene. But whereas the sequence in the first family had originated in chromosome 8, now he found that the translocated fragment came from chromosome 4. The borders of the breakpoints were different, but they appeared to have similar effects.

"We had shown that in the first family, the translocation had lowered the amount of RNA and protein produced by the PTHLH gene, and that was happening in this case, too," Philipp says. "We were already looking at the right type of cell – chondrocytes that we had obtained by transforming fibroblasts obtained from skin biopsies."

Philipp reasoned that the translocations must have disrupted the connections between control elements that governed the behavior of genes on the same chromosome; such sequences are called *cis regulatory elements*, or CREs. *Cis* refers to the fact that the genes and the elements are on the same chromosome.

He decided to try to identify CREs responsible for the PTHLH gene. Normally these sequences are located near *promoters*: sequences that serve as docking sites for the molecules that transcribe DNA into RNAs. Initiating this process requires that various proteins including transcription factors bind to the sequence; they recruit an enzyme called an *RNA polymerase*, which does the real work of gluing single nucleotides together into a new RNA molecule.

Promoters are usually close to the gene; CREs can be farther away. "Most scientists have assumed that there needs to be some sort of direct interaction between the sequences of the CREs and the promoter regions," Philipp says. "This means pulling a distant strand of DNA into a sort of loop that puts the two regions close together, probably close enough that a protein or a small group of molecules can bind to both of them. The effect can be to switch a gene such as PTHLH either on or off."

So Philipp embarked on a search for the CREs that governed the behavior of PTHLH. At the same time, he decided to have a look at another gene that was deeply involved in the formation of fingers, toes, and the overall skeleton: *SOX9*. This sequence was located on chromosome 17 rather than 12, but if nothing else, it would provide a control for his experiments with PTHLH.

It was a fateful choice. Without knowing it, Philipp had happened upon a pair of molecules that might open entirely new vistas in scientists' understanding of the control of genes.

In 2010, Fred Luft turned 68 and "was retired" from the direct clinical duties in the Charité university hos-

pital system that he had carried out for nearly 18 years since his arrival in Berlin. Practically speaking, it didn't mean much of a change. He continued to direct the Experimental and Clinical Research Center, a joint project of the Charité and the Max Delbrück Center focused on combining laboratory science with medicine. He also remained head of a scientific education program for clinicians that he had helped establish between the two organizations. And since the MDC doesn't have a mandatory retirement age, he held onto his research group.

Then, as if that weren't enough on a person's plate, Fred decided to take on a new hobby. I found out about it one day when I met one of the administrators of the MDC's PhD program in the hallway.

"You'll never believe who has just applied to the PhD program," she said.

Fred had submitted an application. After a decades-long career as a physician and scientist, he was going back to school. Given his credentials, what could the MDC's PhD program say? So for over a year, most weekday mornings you could find him in the lab, a pipette in his hand, doing basic bench work.

He joined the research group of Thomas Sommer, whose work involves the way the cell controls the quality of proteins it produces. Cells tolerate so much variety in the genetic code because over more than a billion years, they have evolved mechanisms to detect problems and counteract them. Serious variations – and even random accidents – often produce proteins that have unusual shapes and chemistry. Without a means of noticing problems and destroying such molecules, at least in most cases, cells would likely never be viable. Thomas' lab is helping to unravel the system by which they cope with defective proteins.

The work was interesting, Fred says, but as it turns out, he'll probably never finish his PhD. The last thing he needs, as any of his colleagues will tell you, is another

title, honor, or certificate on the wall. (No, he doesn't really put them on the wall.) So why go to the trouble?

And if you truly want to understand the size of the gap that remains between medicine and the molecular sciences, you not only have to direct a project that inexorably brings the two fields into direct contact. You also have to witness it from both perspectives, first-hand, which for Fred meant going into the lab and learning the same stuff that Philipp, Sylvia, and Atakan had been through.

"To be honest, technically, I wasn't worth a damn," Fred says. "However, I read the cell biology textbook front-to-back and learned a lot of technical things first-hand that are now helping me on our project."

Figuring out whether and how two translocations had caused a disruption of the genes that build normal-sized skeletons and fingers required Philipp and his colleagues to dip deeply into the architecture of genomic DNA. In practice, the molecule never really resembles the elegant double helix found in textbooks. It can be seen

Philipp Maass and Eireen Bartels-Klein

under the electron microscope using special techniques of preparation; during interphase the double strand is barely discernible as the thinnest of threads, wrapped at regular intervals around bead-like structures called *nucleosomes*.

These objects are composed of four types of proteins called *histones*, and two copies of each are snapped together to make small, bead-like globes. DNA is wrapped around them, making 1.67 turns around each one, which takes about 147 base pairs.

Usually these sequences are tied up in such a way that they can't be activated for use in the production of RNA molecules. That may require shoving the nucleosomes out of the way, and here the histones play a crucial role. They have long tails that hang outside the cluster, where they can come into contact with other molecules. The tails have a structure that permits other molecules to attach chemical tags such as *methyl* or *acetyl* groups, a process which determines whether a sequence can be activated or not.

Researchers have learned quite a bit about the changes in histones that permit a gene to be switched on, and Philipp could use that information to search for cis-regulatory elements linked to PTHLH or SOX9. He carried out an experiment to search for such CREs as well as RNA polymerase II enzymes attached to DNA. He also scanned the sequence for sites where transcription factors or other proteins could bind.

The idea that CREs had to loop around and come into close contact with their promoters made it possible to artificially capture strands of DNA that had been brought close to the promoter. By doing so, Philipp identified nine CREs on chromosome 12 that seemed to be involved in the regulation of PTHLH, and four on chromosome 17 related to SOX9. In each case, three CREs gave the strongest "signal" – they seemed most important – so he decided to follow up on them with the help of Irene Hollfinger.

One of the sites on 12 was incredibly far away from the gene. It was so far, in fact, that it lay across the central region of the chromosome, called the *centromere*, on the long arm. PTHLH lies 24 *million* base pairs away (24 megabases) – on the short arm. One of the SOX9 regions that was revealed lay 2.74 megabases away.

This was an amazing finding, one that even Philipp had trouble believing. As far as he knew, the most distant CRE so far discovered lay about 1 megabase from the gene that it controlled. Demonstrating that interactions could happen over such immense distances would require much more proof.

Another finding was even more bizarre. Philipp had used a method called *chromosome conformation capture* to detect the distant CRE for PTHLH. It was like attaching a bit of glue to the PTHLH promoter and watching what got stuck to it. One thing it had pulled down was the sequence from the other arm of the chromosome.

But it also pulled in a loop from chromosome 17 – a promoter for SOX9! In other words, a sequence on chromosome 12 was not only controlling the status of PTHLH; somehow, it was also looping around to come in contact with a sequence on an entirely different chromosome. When that happens between chromosomes that don't belong to the same pair, they are called *in trans* contacts.

Philipp had pulled off the scientific equivalent of casting a fishing lure into a stream and reeling in a whale.

After our return from Turkey, I dropped by the lab every week or so to talk to Sylvia or Atakan or Philipp about how the project was going. I was gearing up to write this book, and they gave me a call when something major happened. About a year after the trip, Philipp and the team were writing up the paper to explain what

Irene Hollfinger

they'd found. He sent me a mail with a request: They were trying to find an acronym or an expression to give to the new phenomenon. He explained the basics of the work to me on the phone and sent me a draft of the new paper. Whatever they chose needed to succinctly sum up the fact that they had found a regulatory element which influenced the activation of genes on two chromosomes.

"The mechanism works *in cis* on chromosome 12, but it also acts *in trans* on the gene on chromosome 17," he said. "Any idea for a catchy name?"

I told him I'd think about it and get back to him. I looked at the draft and played around with combinations of words and letters. Maybe I'd told him about the time I'd had to provide an acronym for a grant we were writing to the European Union; we wanted them to fund continuing education courses for biology teachers. We found a perfect acronym that spelled out everything we wanted to say, but it turned out to be "TESTES". That didn't fly very well with the other members of the consortium, so we had to sit down and come up with something else.

This time it was easier. After a cup of coffee, the name was staring me in the face. I called Philipp's extension.

"Call it CISTR ACT," I said.

"Sister Act?" he laughed. "You mean, the Whoopi Goldberg film?" My kids had watched it at least a dozen times.

"It fits," I said. "*CIS* for the cis interaction, *TR* for the trans, and *ACT* for the activation mechanism, or the fact that it regulates genes on other chromosomes. It also fits because you have something on one chromosome acting in a completely different context to influence another one."

"Like a night club singer joining the nuns," he said. "I'll run it by the group."

A few hours later he called back and said that Fred and the others had given the name their blessing. CISTR-ACT was about to become a term in the scientific literature.

Science writers don't often get the chance to name a new mechanism, a new planet, or a new species. It wasn't nearly as good as having discovered the thing, but it was a nice feeling to have made even a minor contribution to the team's work

In science, extraordinary claims require extraordinary proof, as they say – and CISTR-ACT was certainly an extraordinary claim: first, that a regulatory element could lie so far from a gene, and secondly, that the same element could control genes on different chromosomes.

CISTR-ACT was used to refer to the regulatory element on the long arm of chromosome 12, as well as the mechanism. Was it really involved in regulating the use of both PTHLH and SOX9? To find out, Philipp turned for help to Sigrid Tinschert and her colleagues in Dresden. They labeled DNA sequences near CISTR-ACT, the other CREs, and the genes with fluorescent probes and studied the behavior of the strands in interphase cells. Interphase, Philipp reminded me, is a particular stage during the cell cycle where many genes are transcribed into RNA molecules that go on to be translated into proteins.

"During interphase, the histone tails are activated and the RNA polymerase II acts on genes. The chromatin loops are maintained to control tissue-specific gene regulation events." In a few cases, they saw the probes draw so close to each other that they were almost certainly being brought into direct contact.

"This was consistent with an established principle that within tissues, some interactions only need to happen a few times to have the proper effect on tissues," Philipp says. "Still, we needed more proof."

One piece of evidence came when the scientists proved that gene-activating transcription factors actually docked onto the CREs. Another was provided by an experiment which created artificial sequences consisting of the CREs

and the PTHLH and SOX9 genes. This showed that all three of the elements were activating the genes.

It also provided a direct visual image of the CISTR-ACT sequence in contact with SOX9. Philipp not only had biochemical evidence for the "whale" he'd caught – he'd actually seen it, attached to the chromatin "line".

The strongest activation came from CISTR-ACT, which was most distant from PTHLH, and it confirmed that the finding was probably real. Philipp decided to take a closer look at the contents of the region.

He entered part of the sequence into one of the online databases of information about molecules detected in various experiments that had been carried out across the globe. His search revealed that two segments of the CISTR-ACT sequence were being used to make a single RNA molecule. They weren't directly linked to each other – the fragments were separated by code that didn't appear in the RNA. It meant that cells were transcribing the first part into RNA, skipping over the section in between, and adding another section to the RNA based on the sequence of the second region.

The molecule didn't have sufficient information to make a protein; in other words, the cell was producing a *long noncoding RNA molecule*, or lncRNA. Even more interesting, maybe, was the fact that mice and rats also had a CISTR-ACT that produced a closely related lncRNA. This meant that the sequence had been preserved over long periods of evolution, which greatly increased the likelihood that the lncRNA had an important function. Whatever that was, it had probably been maintained as ancient mammals developed into later species such as humans.

What Philipp needed to do now was disrupt the lncRNA encoded in the CRE region and see if this also affected PTHLH. He ordered custom-made small interfering RNAs, or siRNAs, for the lncRNA, PTHLH, and SOX9. (siRNAs were the molecules that had been discovered by Richard Jorgenson, when he had tried to deepen the purple color of petunias and obtained white flowers instead.) Introducing one of the siRNAs into cells would block the production of the complementary molecule, giving Philipp a better view of its influence on the system.

Again, the results proved extremely interesting – he got more than he bargained for. Eliminating the function of the lncRNA caused a drop in the production of proteins from both PTHLH and SOX9. This meant that the noncoding RNA was directly involved in the regulation of the genes.

Now Philipp did the opposite experiments: In the first, he reduced the amount of PTHLH with its complementary siRNA, and then repeated the procedure by lowering the expression of SOX9. "I wasn't sure what would happen," he says, "but it turns out that those two procedures caused the amount of lncRNA from the CISTR-ACT sequence to rise."

I asked him what that meant.

"It shows that the three molecules are working together in some sort of network," he says. "If you change the expression of one, you influence the others."

Further experiments proved that the CISTR-ACT interactions had to take place to produce the lncRNA. When amounts of the molecule were manipulated, there were even broader effects in chondrocytes: changes were seen across an entire network of genes involved in the development of mesenchymal cells and eventually digits. Seven genes were affected on chromosome 17 alone. This might be due to other *trans*- regulatory events; the lncRNA might come in physical contact with promoters for the other genes, or it may influence their activity a bit less directly.

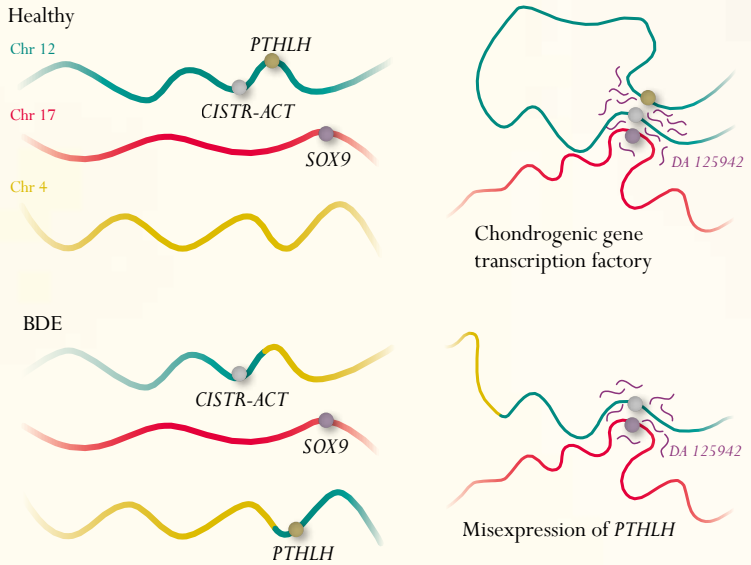
The fact that he was dealing with such a lncRNA was supported by the findings of a young scientist named Ulf Andersson Ørom, working at the Wistar Institute in Philadelphia, Pennsylvania. Ørom had made a presentation in hopes that the MDC would hire him as a group leader. One focus of his work was lncRNA. Other forms of noncoding RNAs, such as microRNAs, had been shown to have powerful effects on the regulation of genes. But little was known about the functions of lncRNAs.

Ørom had shown that many of these molecules were transcribed from sequences lying near the promoters of genes, and they could have an impact on gene activation. Sometimes the same sequence and the same lncRNA could influence different genes.

So why do the families develop short fingers, and have a shorter overall skeletal structure? Philipp thinks that the problem is likely due to a change in the architecture of the chromosomes caused by the translocation events in each family.

"Somehow the rearranged chromosomes – and quite possibly the inversion in the Turkish family – make it difficult or impossible for the cell to arrange its loops and bring CISTR-ACT into contact with the promoters for finger-building genes," he says. "If these regions fail to come into contact with each other, cells produce too much of the lncRNA. As a result they don't produce enough proteins from the PTHLH and SOX9 genes at the right time. Those molecules need to be there so that an entire network of skeletal-building and finger-building genes are activated at the right times during development."

Philipp had shown for the first time ever that a Mendelian disease based on a rearranged genome is caused by dysregulation of genes and lncRNA. "This fact widens the complexity of monogenic diseases," Philipp says, "since it wasn't known that far distant regulatory elements like CISTR-ACT exist and can be also dysregulated."



More evidence for the hypothesis came when the lab showed that the lncRNA from CISTR-ACT directly binds to promoters of the PTHLH and SOX9 genes. In cells derived from brachydactyly patients, this happened at only about half the normal rate. That's what you would expect to see, Philipp says, because people with the short fingers still have one chromosome with the "healthy" structure. It can produce the lncRNA, but the amounts aren't sufficient to build "standard" fingers.

Mice are the mammal of choice in most laboratory models of human disease. They also produce PTHLH, SOX9, and the lncRNA in CISTR-ACT. This has given the lab the chance to pursue the functions of the molecules and the network using the highly-developed tools of genetic engineers. They have already worked out some of the details of the way the system works in what Philipp calls "a chondrogenic transcription factory."

On December 7, 2012, the Max Delbrück Center for Molecular Medicine held a ceremony on the Berlin-Buch campus to celebrate its 20th anniversary. The German Minister of Education and Science made an appearance and gave a speech in which she remarked upon the MDC's surprising trajectory. In less than two decades, the institute had gone from a set of fledgling research projects scattered among half-renovated labs and offices squeezed alongside clinics to one of the most highly recognized research institutes in the world.

Most of the visitors realized that the MDC hadn't appeared *de novo* in Berlin-Buch: like other institutes founded on the campus, it had profited from previous decades of scientific work on the campus. And the MDC had had something else going for it: the magnetic, inspiring personalities of "founding fathers" such as Fred Luft and Detlev Ganten, who had motivated many young, talented scientists to give up promising careers elsewhere and come to Berlin.

That evening, on the top floor of the former Robert Rössle Clinic, most of the major figures of this book met for a reunion. Atakan Aydin had organized a sumptuous buffet of Turkish food from a Berlin caterer. In a side-room, a video of the first trip to Turkey played, and a beamer displayed photographs that had been taken over the entire history of the project.

I didn't realize it until that moment, but these people had never been in one room as a group at the same time. The normal comings-and-goings of scientists over

twenty years had phased in some members of the group just as others had left. Hakan Toka had flown in from the United States and Okan from Erlangen; I had never seen the brothers, whose lives were so deeply entertwined, together. Thomas Wienker arrived late, but he came – his first meeting with some of his former colleagues in over a decade. New members of the group got to meet the people who, long ago, had started the project they were still working on. Sylvia introduced me to Jens Tank and Evi Jeschke, whom I had never met.

The only significant figures missing were Ramin Naraghi, who had planned to come but couldn't make it, Nihat Bilginturan (whose health didn't permit a long flight), and, sadly, members of the Turkish family whose health problems had prompted the work in the first place. But they would likely come soon; plans were being made to bring another group to Berlin sometime in the New Year.

Fred gave a short presentation in which he covered the history of the project and the latest findings, which were new to many of the people in the room. After a decade in which the work had proceeded with aching slowness, Philipp's project had made a great stride forward in explaining the family's short fingers. And the deep sequencing project initiated by Sylvia, Atakan and the others seemed set to expose a variation in a gene that might finally yield insights into hypertension. It has never been completely clear, Fred pointed out, whether the two features stemmed from a single genetic defect or two separate ones that lay so close together on the genome that they had been passed down together for at least six generations in Kemal's family.

At the close of his talk, Fred raised several questions that the group now faces: do the rearrangements that disrupt the architecture of chromosomes, such as gene regulation by CISTR-ACT, also play a role in Bilgituran's syndrome? It's very likely, he says. It can't be an accident that the region near the PTHLH gene, affected by translocations, has undergone an inversion in the Turkish family. After all, that inversion produces fingers that are indistinguishable from the brachydactyly found in the families in Dresden and Potsdam. Something else is going on to produce the hypertension – maybe something similar, maybe not. But we have data, he says; we know what to do next. The next edition of this book will take that story farther.

Most of the science carried out in institutes such as the MDC is more straightforward and driven by clear hypotheses that are usually limited in scope. Most medically related work in the fields of molecular biology and genetics starts at the small end of the spectrum, with the investigation of a single gene or a small set of molecules. Such projects have a clear pathway to success: You disrupt those genes in the test tube, in cell cultures, and model organisms; you discover how they affect the building plans of cells and tissues and, if you're lucky, link their effects to a human disease. Most of the papers printed in high-impact scientific journals like *Nature* or *Science* or *Cell* begin that way, and they generate daily headlines. Working the other way around – starting with a family's disease – is usually such a difficult prospect that most scientists wouldn't touch it with a ten-foot pole.

The tidy format of a talk or paper often hides the fact that many scientific accomplishments are the result of years or decades of painstaking work: weeks and months in which researchers repeat the same procedures over and over, hoping to find the locus of a genetic defect, or to narrow it down, or to uncover that one bit of information which will resolve a single question. Scientists know that such discoveries are way-stations along a much longer road: each answer usually opens a vista of new questions. Biologists are only beginning to grasp the basics of the issues raised by CISTR-ACT: how extremely complex interactions within the strands of chromosomes manage the activity of genes, in cells and tissues from our head to toes. The activities of these molecules combine to create the complex structures that build bodies in the first place and maintain their health over the long term.

Understanding why those processes don't work, sometimes in just a few individuals, requires understanding the whole. And everyone in the room knew that reaching this point – the ultimate goal of "molecular medicine" – was still a distant dream.

Achieving it will likely require the development of new concepts such as the recent understanding of the roles of noncoding RNAs, and new technologies like the high-throughput methods that have given scientists their first view of the concerted action of genes, the interplay of chromatin strands, or the complete expression of DNA as RNA and protein molecules. It certainly won't happen in a single step; instead, we surely face many more decades of steady progress, with great breakthroughs that occasionally provide stunning clarity into particular scientific problems. Developing "cures" for genetic conditions will likely take much longer, and will require new types of interactions between disciplines that have developed independently, in some cases, over the past 150 years. One area under intense development is the ability to create models of complex, shifting processes using mathematics and computers. Cells are able to decode the information in their genomes, in collaboration with extraordinarily complex factors in the environment. But without the aid of models and computers, it is unlikely that our brains ever will.

As Fred spoke, it was clear that none of team had had any idea at the outset of the project that it would occupy their days and nights for at least twenty years, or continually take them to the edge of genetic and molecular science. There had never been any guarantee of ultimate success. So much about the entire apparatus of the way today's research is done – with its continual, self-critical demand for results, the need to convince an institute and its advisors of the value of a project, and the need to obtain major funding to carry it out – had posed obstacles during the slow years.

I hope that even if they had been aware of the difficulties ahead, this small, brave group would still have taken those first steps toward understanding Bilginturan's syndrome. Sylvia Bähring put it best, I think, the day she told me that carrying out such a project required complete devotion to a human instinct that forms the basis of science: pure curiosity.

Whatever has happened along the way, Fred and his colleagues have always known that there must be an answer: There must be a reason for the family's short fingers and hypertension. Finding it may take years, or decades, even longer than one scientist's career or lifetime. But such a reason exists, and the harder it is to find, the more interesting the answer is likely to be.

So Kemal's journey, which began over 50 years ago, has not yet come to an end. There is still no definitive answer to his family's problem. But the step he took accomplished great things: It led to Nihat Bilginturan's arrival, who helped the family take a remarkable step forward in their standard of living. The arrival of Fred Luft and his team led to Okan Toka's drug study, and continual contact with physicians who have extended the lives of affected individuals by decades, with the help of donations from pharmaceutical companies. The work of Kemal's son Cafer is helping the community come to grips with a fast-moving modern world, while trying to hold on to the lifestyle and values that they treasure. And perhaps, one day, there will also be a better medical solution for the syndrome that affected Kemal and will continue to be a part of his family for many generations to come.

Afterword by Nihat Bilginturan

I completed my residency program in 1960 at Hacettepe Children's Hospital. From 1960 – 1961 I worked as a chief resident in the same institution. Afterwards I went to the USA for training in pediatric endocrinology. For the first year, between 1961-1962, I worked with Dr. Angelo M. DiGeorge at St. Christopher's Hospital for Children which is connected with Temple University in Philadelphia.

During the first day of my arrival, the lunch menu in the hospital cafeteria was pork. The food server told me that he could not give me pork because I was a Muslim; they had prepared a special menu with chicken for me. I told him that although I am Muslim, I am not a strict Muslim, I may eat pork. So he gave me the pork menu.

I didn't know anyone except my future boss, Dr. DiGeorge. I sat down at the table across from him. He introduced me to a colleague, a pediatric nephrologist on the staff. I was getting ready to eat when the nephrologist told me, "You are not supposed to eat pork because you are a Muslim." I answered him, "Yes, I am a Muslim, but not a strict one." The nephrologist looked at me sternly and said, "No, you are Muslim, there is no such thing as strict or loose; you are Muslim and you are not supposed to eat this pork." I stopped eating and I was disappointed. Dr. DiGeorge told me, "Why don't you ask him why he is eating pork?" I said why he wasn't supposed to. Dr. DiGeorge said, "He's a Jew." So we all laughed and I finally started to eat.

One-and-a-half months later, in the middle of August, I was doing a test on one of my patients. All of the staff of the hospital one by one, were supposed to stop by and have a look. The last person to come by was Dr. Arey, a professor of pathology, and as he passed by he asked me, "Dr. Bilginturan, what do you think about that patient?" I told him that I don't know the patient. He took me to the patient's room and told to the resident to give me

some information about his patient. She was a 13-year-old female with high fever and petechial skin lesions. I asked Dr. Arey, "Can't you make a diagnosis for that patient?" He said no. I said, "This patient has Rocky Mountain Spotted Fever."

I asked the resident if the girl had gone to summer camp. The resident became red in the face and said she had attended Pocono's camp, on Pocono Mountain, an extension of the Rocky Mountains. Dr. Arey asked what we needed to do for a proper diagnosis. I answered that we should take blood for antibody titer and repeat it in 2 weeks. If the titer is elevated, the diagnosis is Rocky Mountain Spotted Fever.

A month later during one of the grand rounds, the resident discussed the case. All of the staff were present, including Dr. Waldo E. Nelson, the chairman of pediatrics. The resident said, "All of you, including Dr. Nelson, saw the patient and were unable to make a diagnosis. The honor of the diagnosis belongs to Dr. Bilginturan. Dr. Nelson turned to me and asked, "Dr. Bilginturan can you talk about Rocky Mountain Spotted Fever to us?"

I said, "Dr. Nelson I don't know much about this disease; it's native to your country." He was astonished that I should come from Turkey and diagnose "their disease." After this presentation, my credit rose a hundred-fold in the department.

A few months later I told Dr. DiGeorge I would not be staying with him the next year. He asked why not. I told him that I wasn't satisfied with his training. Perhaps he could give me names of a few centers which provide good training in endocrinology. He gave the name of Dr. John F. Crigler (Harvard University) and Dr. Stemphel (University of North Carolina) and another name from New York University. I asked him whether he would give references to me for those centers. He said I will give you my best reference. For the second reference I asked Gene Klinberg, who had worked at Hacettepe University for 2 years during my residency training. He gave really the best reference for me.

A few weeks later a contract came from Harvard University prepared in my name. I signed it and sent it back. In May 1962, there was a pediatric meeting in Atlantic City. In the meeting I met with Dr. Crigler and I introduced myself to him. He said, "I am very glad to meet you." He took me to a sea food restaurant. During this lunch I asked, "You sent me a contract without an interview, why?" He said, "Your references were so good that I did not feel the need to do an interview with you."

So on July 1, 1962, I went to Boston, I started to work with Dr. Crigler at the Children's Medical Center, which is connected to Harvard University. I worked with Dr. Crigler for 2 years between 1962 – 1964. 2 weeks after I started to work in the hospital, Dr. Crigler invited me to dinner at his house. He didn't mention an exact time. I went to his house a few hours before dinner.

When I entered the salon they were playing chamber music. Dr. Crigler was playing cello, his wife flute, his daughter piano and his son violin. After they finished their music, he asked, "Dr. Bilginturan, which instrument do you play?" I felt ashamed. I answered him I play a Turkish instrument named the "Kanun". He asked what kind of instrument this was. I answered, "There are 64 strings and several tuning pegs." He said, "I will try to find a 'Kanun' and I will be happy to listen to you." I was uneasy for 2 years, worrying that he would actually find a "Kanun" and ask me to play, but he didn't find one… Back in Turkey I took a "Kanun" course, just in case, to feel better about myself.

Another time we were going somewhere in his car. Classical music was playing on the radio. He was asking himself what was it. I told him that it was "Scheherazade" by Rimsky-Korsakov. He said, "How do you know?" I told him that in Turkey we listened to classical music, we went

to concerts of ballet and opera. In the beginning of my second year I was working in my laboratory and listening to classical music on my radio. One day I had to go to downtown and I asked Dr. Crigler if he could keep an eye on my work in the laboratory for a couple of hours. He said, of course. When I came back from downtown, the radio was playing a piano concerto. Dr. Crigler said, "This is a piano concerto by Haydn." I said no, "This is by Mozart." We made a bet for five dollars. At the end of the concerto, the speaker announced that we had been listening to a piano concerto by Mozart. I took his five dollars, and after the discussion he gave me a season ticket to the Boston Symphony concert series.

At the end of two years, when I was ready to turn back to Turkey, Dr. Crigler told me, "Don't go back to Turkey. I will give you a good position here." I said I had to return to carry out my obligatory military service. He asked how long it would take. I said two years. He said, "Okay, you go to Turkey, finish your military service and come back to Boston. Your position will be ready then." So I returned to Ankara for my military service. At that time I stopped by Hacettepe Children's Hospital, where I met with Prof. Dr. Ihsan Dogramaci, my boss. He took me to his office and engaged in a bit of brainwashing. He persuaded me to stay at Hacettepe before my military service. I started to work at Hacettepe University as a Pediatric Endocrinologist. In 1966 I received a position as Associate Professor. Then I took my military service between 1967 – 1969 for two years.

In the beginning of 1970 I returned to Hacettepe University and was assigned Head of the Children's Hospital. During this time I was involved with a genetic disease with the symptoms of brachydactyly and hypertension. One day Kemal and Mutebeer brought a child to my office. I examined the child. He had a first- and second-degree heart murmur. I took the heart X-ray, which showed a normal heart size. I told the family that at the present time everything was normal. "It looks like an innocent murmur, but we'll have to follow up him yearly."

As I investigated the child I noticed that the man and the woman had short stature and a coarse body structure. In addition, they had very short fingers. When I tried to investigate more, they told me that they also had high blood pressure. The affected individuals all died at 40 – 45 years of age from cerebral incidents. They said that there were many affected individuals in the village (Karamat).

I tried to get a short family pedigree. Even from this quick discussion I was sure that the short fingers and hypertension were symptoms of an autosomal dominant disease. I decided to go to their village. I said to Kemal – who was called a Hafiz, because he knew the Qur'an by memory – "I will come to your village and will see all the affected individuals."

A few months later I sent a letter to Kemal saying that I would come and I would stay one week to examine those patients. I took a photographer with me. We went together to a city very close to Karamat (the affected patients were living in this village). It was a rainy day, and we couldn't find any vehicle to go to Karamat. The road was out of order because of the rain. No ordinary vehicle could make the trip. They told me that we needed to find a 4-wheel-drive vehicle to go. After a long search we found that the hospital connected with the ministry of health had a 4-wheel-drive vehicle. We found the responsible physician, whose name was Ibrahim, and I told him that only his vehicle could go to Karamat.

He called his driver, Selahattin, and told him that he should drive "the doctor and his associate to Karamat." Selahattin said, "I cannot go to Karamat." But Dr. Ibrahim insisted that he go. Selahattin said, "I will quit my job before I drive up there!" Dr. Ibrahim told him to bring the vehicle, and that he would take us to the village himself.

During the drive to Karamat there was a heavy rain. Along the way we had to stop the vehicle because the road

was washed out. The photographer and I got of the car and jumped out and pushed until the car turned around. We decided to wait in the car until the rain stopped. In this interim a man on the back of a mule was going up. I asked him where he was going. He said, "I am going to Karamat."

I explained our problem. "Please kindly tell the Hafız he must bring 2 mules to us so we can go to Karamat." The man asked, "Where you are going to stay in Karamat?" I told him we would stay in the Hafız's house. He said, "The Hafız is a poor man, you can not stay there." But I insisted we had to stay there, and that he should please tell Kemal to come and pick us up.

A couple hours later, the Hafız appeared on the back of a mule, accompanied by two other mules, and came and took us to Karamat. His house had one bedroom and a big kitchen. The family spent their time in the kitchen, ate there; they made their corn bread and everything else in the kitchen. There was one very small extra room near the entrance. The extra room was full of stuff they weren't using, and that's where we would stay.

We ate our dinner and we went to sleep. I slept on a bed and the photographer slept on a cot set up on the floor. The next morning, after breakfast, the Hafız told me our room was ready to work, and he took me to the small room. At night they had cleaned out the room and they had put in a table and four chairs. He told me all of the people of the village had assembled and were ready outside the house.

I examined all the people, both normal and affected. I measured the height, weight, and upper-lower body ratio. The photographer took their pictures (close-ups of their faces, hands, feet, and an overall body shot). I found almost 55 affected individuals and I drew up a family pedigree. Three days later we returned back to Ankara.

A few weeks later we invited a group of five or six affected individuals, males and females from Karamat. We admitted them to the internal medicine department. We took X-rays of the body (especially hands, feet and skull) and we did a hypertensive workup. At the end of our investigation we couldn't find any specific cause for their hypertension. We summarized our findings in a scientific paper entitled "Hereditary Brachydactyly and Hypertension," which was published in the September 1973 issue of the *Journal of Medical Genetics.*

In 1971, I was appointed full professor. In the same year I was involved with another genetic disease. One day a man came to my office at Hacettepe University. His name was He said that he had 13 children, all of whom had died in the first one or two months of their lives due to high fever, seizures, vomiting and diarrhea. "Now my wife is pregnant, in the next two weeks she will deliver a baby," he told me. "I want this baby to be alive. Please help me." I said I would do my best.

With the hospital ambulance, one gynecologist and one pediatrician, we went to his village "Yukarı Karabag" (it is Ayfon Karahisar City's village). And they brought the pregnant woman, whom we admitted to the gynecology service. In this interim I drew a short family pedigree. The father and mother were close relatives. And in their village there were 45 families with the same problems, who had lost 10 to 15 children with the same problems.

After getting this information, my colleague Dr. Özand (a biochemist) and I started to search the literature to find any cases published similar to our patient. Finally we found a paper with same problem: A child had died at an early age with high fever, convulsions, vomiting and diarrhea. While the child was alive they couldn't make a diagnosis. During a postmortem investigation they took different organ biopsies. From those biopsies they found a deficiency in an enzyme called *leukocyte acid phosphatase*. Now we took blood from the expecting mother, from the umbilical cord, and later from the baby. After a long investigation, my colleague Dr. Özand found a leukocyte

acid phosphatase deficiency in that baby as well. We tried enzyme induction with prednisone, and gradually the child's enzyme levels became normal.

We kept the child in the hospital for one year until we believed that everything was normal. We discharged him at the age of one year. His father gave the name "Yasar" (which means alive). One year later, the same man came to my office and said that his wife was pregnant again. We admitted his wife and she delivered a male baby, who also had the enzyme deficiency. We did the enzyme induction with prednisone and discharged the baby at the age of one month. His father gave him my name, "Nihat". At the present time he and his older brother are still alive.

In July 1973 there was a Diabetes Meeting in Brussels, Belgium, where I met Dr. Robert L. Jackson. He was impressed by my presentation and he asked to talk with me. We got together in a cafeteria. He said, "I am a Professor in pediatrics and head of the Pediatric Diabetes section at Missouri University in Columbia, USA. I will retire in a couple years. I want you to take over my job."

I told him that for the job I needed a green card; I knew it was difficult to get one and it took a very long time. Dr. Jackson told me that he would send me a green card in 10 days. I said, "How?" He said that the Missouri Senators were close friends of his, "I can arrange it."

Ten or fifteen days after I returned to Turkey from Belgium, I received a phone call from the American Embassy in Ankara. They said that my green card was ready. I went to the embassy and got the permits (for me, my wife and sons). I took two years of my sabbatical, went to the USA, and worked for two and a half years (from February 1974 to July 1976). Then I was ready to return to Turkey. Dr. Jackson told me I shouldn't go back, "Stay here and take over my job." I told him that if he could give me tenure, I would be glad to take the position. But the chairman of pediatrics, Dr. Barbero, told me that it wasn't possible to give me a tenured position. So I returned to Turkey and started working again at Hacettepe University.

In the early 1980s, I saw an announcement in the *New England Journal of Medicine*. King Faisal University in Saudi Arabia, was looking for physicians with various areas of specialty: medicine, surgery, pediatrics and so on. I applied there and I was invited to Dahran (a city located in the eastern part of Saudi Arabia) for interview. They sent me a first-class ticket; I went to Saudi Arabia, to Al-Khobar city, in which the King Faisal University Hospital was located. After an interview with Dean of the medical school and vice-rector of the university I signed a contract for 2 years. At the end of two years I extended my contract for another two years. All together I stayed in Saudi Arabia between 1982 – 1986. Then I returned to Turkey and started to work at Hacettepe University. I retired in 1999 and started to work in my private practice as a pediatric endocrinologist. In 2010 and 2011 I had two serious operations and I ended my private practice.

Afterword by Friedrich C. Luft

Why we do what we do

I trained as a clinician but have spent over 40 years dabbling in science. I spend my time bungling and bumbling around in very dark rooms trying to catch black cats that may or may not even be there. Of course, I cannot leak that fact into any grant applications. Grant applications are formulated into puzzles and are directed at "peer reviewers". Grants must be reductionist in nature, hypothesis-testing if you will. Every little idea must be laid out like a "straw man" that you should do your best to knock down, hoping he'll weather your barrage of experiments, but you stand ready with a backup plan if he goes down. This process runs counter to most of what we do in science, which is not a process of solving jigsaw puzzles. Nature doesn't provide a picture on the box, nor a guarantee that you have all the pieces; they aren't machine-cut, so it's often hard to tell whether two pieces really fit, and you have no idea what shape will appear when you assemble them all. Probably not a rectangle. You don't find many perfect right angles in nature.

My career has consisted of writing the next paper so that I can then have success with the next grant, because no paper means no grant and vice versa. It's a game of chicken-and-egg, sometimes quite vicious, but refusing to play may well bring your career in academic medicine to an end. Once, as a matter of fact, the threat of such an impasse caused me to switch countries. The failure to get a grant can put someone is out of a job – if not me, then someone on my research team.

Nonetheless, I love what I do, but never have questioned, "why"? Now that the end of my career is neigh, I have had occasion to ponder this question. A small booklet entitled *Ignorance – How It Drives Science* has helped me in that regard.

In his book, Stuart Firestein draws attention to a very elucidative comment by Donald H. Rumsfeld, former US defense secretary and who lies, on the human spectrum,

about as far away from a scientist as anyone you could imagine. When questioned about his bungling of the Iraq war, Rumsfeld uttered, "there are known unknowns and unknown unknowns". It's tortured locution, but for once Rumsfeld had gotten it right – not in reference to Iraq, but to science. Science actually disappeared from Western Civilization for a period after the fall of Rome ("The rise of barbarism and religion," to steal from Edward Gibbon). After all, there were no more unknown unknowns. All the unknowns were answered in The Gospels, Aristotle, or Galen, or if any unknowns remained, their answers should be sought in these writings. It must have been a pacific and soporific millennium, at least mentally. Nevertheless, Francis Bacon, Jean Jacque Rousseau, and other visionaries managed to lay a new foundation for examining questions that brought back the fact that unknown unknowns are our drivers. In short order, Galileo, Copernicus, Newton, Leibniz, and a host of other geniuses added tons of unknown unknowns.

My associates and I, on a much more modest scale, have attempted to join such adventurers. Our model story is that of the Argonauts rather than the Odyssey, merely because Jason sought the Golden Fleece along the Black Sea coast in Colchis, not too far away from modern-day Trabzon. Our adventures have not been quite as dramatic as those of the early Greek heroes, but we seem to be taking about as long. Now, where is the science in our story?

Our project was largely an assignment, "Your job is to do molecular genetics related to hypertension," my new boss explained when I started working in Berlin. I had little experience in molecular biology and no formal training in genetics. However, I had opportunity on my side. Thomas Wienker, a real geneticist, first drew my attention to the publication leading to our project. The Toka brothers explained that Turkey, a country completely unknown to me, could be not only mastered but also enjoyed. Herbert Schuster and then Sylvia Bähring explained that molecular biology could also be learned and mastered, even by me. Edison once wryly observed, "Opportunity is missed by most people because it is dressed in overalls and looks like hard work." But hard work had never been a nemesis for me. And then Nihat Bilginturan, finding that our motives were appropriate, unlocked the key to the families that have become our friends.

I knew what linkage was, and finding out where the genetic problem of this family lies was unraveling an unknown; reductionist approaches helped us here. However, the unknown unknowns are far more difficult. Firestein draws attention to an aphorism by the biologist and evolutionary scientist J.B.S. Haldane, who observed, "Not only is the universe queerer than we suppose; it is queerer than we *can* suppose." The universe of our lab, which has been genetics and its oddities, continues to be unraveled by others, giving us the ability to suppose more and more as the technology advances. After all, we had positional cloning as a strategy, and Sylvia attacked the known genes and unknown DNA structures one at a time. She spent a year on SOX5, a likely candidate because it is a transcription factor involved in skeletal development. However, the forms of SOX5 in the family yielded no mutations. We received a tip from a colleague that a splice variant existed, a particularly long form of the protein termed L-SOX5, which is expressed in chondrogenesis. I believed that this gene must surely be it. Another group beat us to a publication on the entire L-SOX5 structure, meaning that there was no reward for two-years of hard work; nor for the grant that supported it. However, once again I came to grips with unknown unknowns, having never even heard of splice variants and how they work prior to the project.

Are there limits? Is our problem even solvable? Firestein draws attention to this possibility in a chapter entitled, "Uncertainty, Impossibility, and Other Minor Problems." Surely our problem cannot be solved without new tools. But new technology has come along with a vengeance. When we started our adventure, the human genome

project had been underway for a mere four years. After another six years and about $3 billion later, the project was finished, but it did not help us much. Nevertheless, it may now do so. The cost of obtaining the entire genomes of our subjects has fallen to about $5000 per head, and the costs will fall even farther. This tremendous advance could not have been foreseen at the time.

The quality of our ignorance has also surely improved. We have spent five years and several grant cycles chasing down a microRNA. The very concept of a microRNA hardly existed a decade ago, a solid member of the club of unknown unknowns. We found that our microRNA (published), when expressed in various cell lines, influences pathways and networks involved in cell growth, proliferation, collagen synthesis and development pathways highly germane to our project (unpublished). We believe that this microRNA or another noncoding RNA exist; however, they could still be a figment of our imagination, a spurious finding, an error, artifact, or it could even lie outside our linkage interval. We do not know for certain - more unknown unknowns. However, all questions are interesting if they lead to and connect with other interesting questions, and here our project has been a bonanza.

Our project has been a clinical adventure as well, which makes it particularly great for clinical science. We have dwelt with anatomy, physiology, neurophysiology, clinical pharmacology, metabolism, and vascular biology in the several visits our subjects have made to Berlin and the visits we have made to them. Each of these endeavors has raised unexpected unknown unknowns. Should our subjects undergo neurosurgery to relieve the pressure from a blood vessel that makes contact with the rostral venterolateral medulla? A host of data suggests that this area controls how the autonomic nervous system regulates blood pressure. A relatively brief, well-established neurosurgical operation could perhaps cure the subjects, or so believes Ramin Naraghi, another of our partners. I am skeptical; after all, I would not operate on their fingers to lower their blood pressure. But possibly, I am merely a troglodyte, an impediment that should just get out of the way.

I know that Stuart Firestein must write grants to fund his research, just like I do. I was struck and relieved by his comments on *hypotheses*. The hypothesis is supposed to be the starting point for all experiments; ask any granting study section. If the word *hypothesis* does not appear in your grant and is not followed by three concise, specific aims, including alternative strategies, your grant has about the same chance of bringing home money as a snowball has of surviving in hell. We were all brought up that way and must react that way or find a nice medical practice someplace. The hypothesis is a statement laying out what one does not know and is then followed by a strategy for finding it out. "Scientists get behind one hypothesis or another as if they were sports teams or nationalities, or religions," explains Firestein, who hates hypotheses. Amen to that! He sees them as imprisoning, biasing, and discriminatory. I had not known this, but Newton once said, "Hypotheses non fingo" ("I frame no hypotheses"). Well then, no grant money will be coming to him! In terms of our project, I guess we are chasing God's hypothesis, surely not one from the likes of me.

I believe most scientific discoveries are accidents. Fleming's *Penicillium* mold blew in from the window. Scientists have the privilege of living from accidents; but just try that idea on lawyers or politicians! A prepared mind is no hindrance and the best preparation for my students' minds, I have felt, is to fill them with curiosity. Curiosity is even better than having memorized all the papers in *Cell* or in the *New England Journal of Medicine*. Curiosity drove Philipp Maass when he found that short fingers could result from a balanced translocation. The chromosomal shift had moved a critical component out of place, rather than destroying a gene or creating a new one. His persistence, and several years of hard work, ultimately led to the discovery of a novel chromatin regulatory

mechanism that not only involves the chromosome on which the regulator resides, but also involves a far distant chromosome. Russ Hodge coined the term CISTR-ACT (or "Sister Act") for "cis and trans-chromosomal communicator acting through DNA and noncoding RNA on gene regulation". So now a happy African-American nun borrowed from the film genre is doing her mischief across the human genome.

We know from our research that a black cat resides within our dark room, although we have not found it yet. Not all scientists are lucky enough even to know that their black cat exists. Try the "string-theory" physicists or those working on the 11th dimension. However, what if somewhere in the past, we have blundered in our work to the point that we have no hope finding our cat, irrespective of how much groping around we do? That indeed is a risk that probably confronts all scientists. After all, some good ideas are also just wrong. Dumb and ignorant are not the same thing. We can aspire to ignorance but we cannot afford to be dumb. Thus, we continually back-check our work and in so doing are driven to pursue old leads.

Earlier I mentioned uncertainty. Werner Heisenberg maintained that there is a fundamental limit to the precision by which certain physical properties can be known simultaneously. The notion is a bit difficult for non-quantum mechanics to grasp. Erwin Schrödinger developed a spoof on the uncertainty principle involving a cat. The scenario presents a cat that might be alive or dead, depending on an earlier random event. Quantum mechanics implies that the cat is simultaneously alive and dead. However, recent work suggests that Heisenberg's uncertainty principle is getting less certain. There are reports that entangled photons can be measured. So Erwin Schrödinger may have the last laugh. After all, he said, "In an honest search for knowledge, you often must abide by ignorance for an indefinite period."

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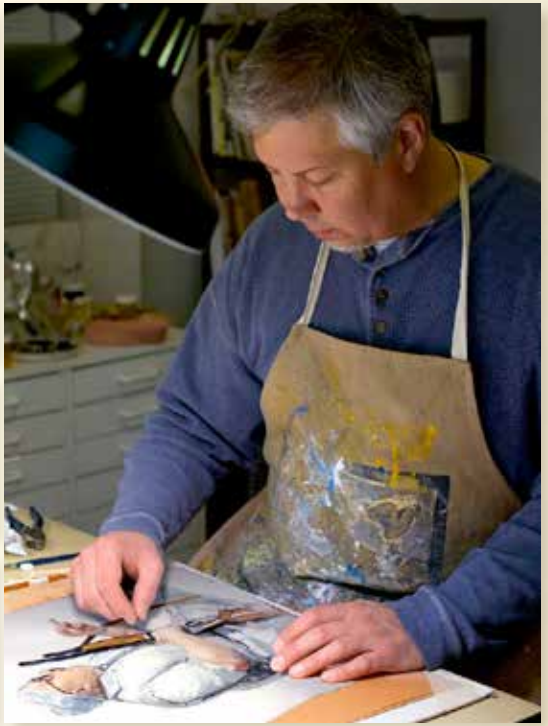








Russ Hodge

Yvette Wefeld-Neuenfeld, Eireen Bartels-Klein, Irene Hollfinger, Astrid Mühl

Hakan Toka

Fred Luft

Okan Toka

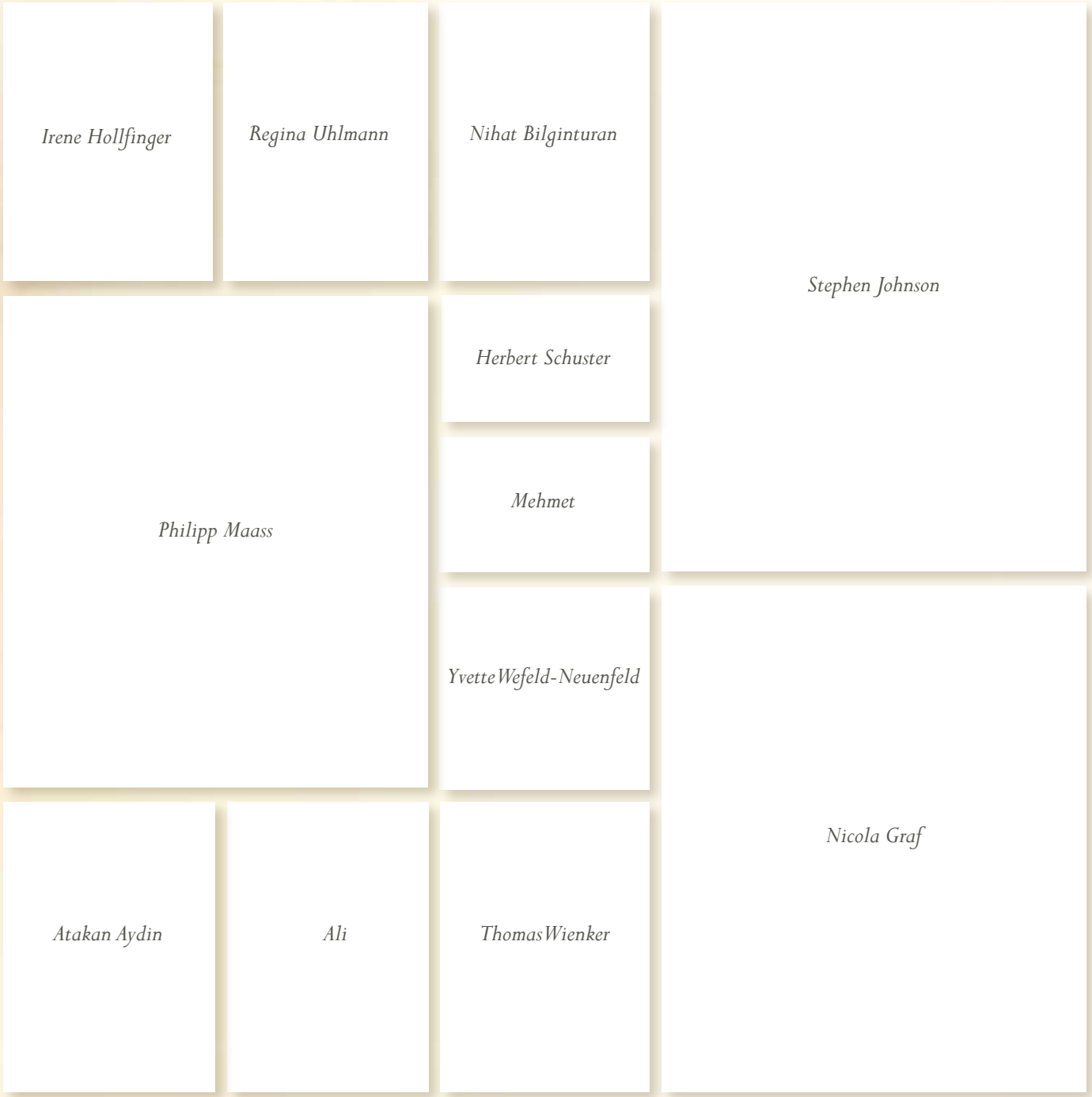
Maj Britt Hansen

Sylvia Bähring

Astrid Mühl

Eva Jeschke

Maolian Gong


Irene Hollfinger
Regina Uhlmann
Nihat Bilginturan
Stephen Johnson
Herbert Schuster
Philipp Maass
Mehmet
Yvette Wefeld-Neuenfeld
Nicola Graf
Atakan Aydin
Ali
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