

SPOAN

Consanguineous marriages bring about an unknown form of deficiency in a small town in the Northeast of Brazil

a new illness

MARCOS PIVETTA,
FROM SERRINHA DOS PINTOS
(RIO GRANDE DO NORTE)

PHOTOGRAPHS BY EDUARDO CESAR

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S

ome fifteen years ago Elenara Maria de Queiroz Moura was pregnant—and a scene from a soap opera would not go out of her head. A couple who were cousins wanted to have children and looked for a gynecologist. When he knew that his patients were kin, the television soap opera doctor was tacit: it's better to avoid a pregnancy. Consanguineous marriages show a higher risk of generating children with some kind of hereditary disorder. If you want to have descendants, it would be more prudent to adopt one, the doctor sentenced. Elenara, at that time 20 years old, had reasons for being worried. She was married to José Moura Sobrinho, a first cousin some five years her elder. Both were natives of Serrinha dos Pintos, a municipality of 4,300 inhabitants, some 370 km to the west of the state capital Natal, in the state of Rio Grande do Norte, where marrying a relative is a local custom. And there were in the family “handicapped”, uncles confined to wheel chairs due to a mysterious disorder, which, little by little, stiffens the joints and then weakens first the legs and then the arms, as well as affecting posture in general, and to a lesser degree, vision and speech. In spite of her fears, Isabela, the couple's first born, was born normal. “I was relieved and thought that everything was alright”, Elenara recalls. “I became pregnant with my second child without having



Sundown in the town center
of Serrinha dos Pintos:
a town of the Queiroz, Dias
and Fernandes families

any fear” But the story of Paulinha, the ten-year old younger child, was different.

The girl was born with the SPOAN syndrome, a neurodegenerative disorder recently discovered among the inhabitants of the small town and described in May by researchers from the Human Genome Studies Center of the Clinical Hospital of the University of São Paulo (USP) in an article published in the North American journal *Annals of Neurology*. As yet it is unknown on which gene the mutation occurs that causes the disorder, but the scientists have analyzed DNA samples of 74 of the town’s inhabitants, among the sick and the healthy, and the results of the study indicate that the SPOAN gene can be found in the region of chromosome 11. The problem is that there exist at least 143 genes in this region, of which 96 are active in nerve tissue. Or that is to say, for now, almost one hundred genes are candidates for causing the disorder.

“We’re mapping the gene region or district where it is found”, comments the geneticist Mayana Zatz, the coordinator of the work on the new disorder, who heads up the Human Genome Studies Center, one of the ten Research, Innovation and Diffusion Centers (Cepid) funded through FAPESP. “What’s missing is to find its house, the gene linked to the syndrome.” With luck, in two or three years, the USP team hopes to have isolated the gene and identified the mutation that causes SPOAN. As soon as they have this information, the scientists are going to make a pre-natal test capable of detecting the presence of the mutation in babies still in gestation and identify the heterozygote individuals of this genetic anomaly (healthy people, but who could have children with this disorder). “Up until now there is not a single neurological disorder associated with genes in this region of chromosome 11”, says the doctorate student Lucia Inês Macedo-Souza, given the responsibility of finding the “house” where the molecular base of SPOAN is found.

SPOAN stands for Spastic Paraplegia, Optic Atrophy and Neuropathy, a complex name for a complex disease. For a “family problem”, one is not sim-

ply talking of the inhabitants of Serrinha. Up until now the scientists have identified 26 people living with SPOAN of whom 17 are women and 9 are men. All of the individuals affected are white Caucasians, probably of Portuguese or perhaps Dutch descent, and were born in this hilly town. The majority still live in their native town and all of them are descendants of related couples, from 19 consanguinity unions. “We examined patients of various ages with the syndrome, from 10 to 63 years of age”, says the biologist Silvana Santos, the main person responsible for the unprecedented pathology discovery, who is receiving a post-doctoral grant from FAPESP. “We can see the evolution of the illness. With time, the people close up like a flower.”



Although without a cure, the illness in itself is not fatal and maintains the thinking capacity of the patients intact. It does not bring about mental retardation, pain or deafness. But its effects on the quality of life of those affected, who become physically handicapped, are devastating. Above all in a rural population and one short

of health services such as Serrinha dos Pintos, which believe, in a folklore manner, the origin of the illness to be hereditary syphilis of an ancient and ancestral womenizer that has been spread through family blood (*see chart on page 38*). Here there is no physiotherapy service to minimize the problems of posture coming from the paraplegia associated with the illness and the victims of the syndrome live secluded from day to day happenings, closed up in the inside of their homes, totally dependent on the care of their family. Without due medical attention, nobody takes medicine to reduce the rigidity and the weakening of legs and arms. The feet curl outwards and the head drops. Of the known sick people, only Paulinha is not in a wheelchair. With the interminable energy that only children appear to have, the girl manages to get about with the help of a walker on wheels.

In the jargon of molecular biology, SPOAN classified itself among the heredity recessive autosomal disorders. Men and women have the same proba-

bility of presenting the pathology, in spite of the number of cases known in Serrinha being greater among the female sex. A person will only develop SPOAN if the two copies of the as yet unknown gene associated with the syndrome, one coming from the father and the other from the mother, carry the mutation that leads to the health problem. Therefore the parents of a patient with SPOAN are necessarily heterozygotes. They are carriers of the gene in only one of the two copies of the gene, never in the two, and do not show the syndrome. But they can transmit it to their offspring, as attested to by the Serrinha patients. Sons and daughters of heterozygotes participate involuntarily in a game of biological Russian roulette. There is a 25% risk of becoming ill, of inheriting the two copies of the gene with the mutation; 50% risk of only being a carrier of the mutation in one of the gene copies; and 25% risk of not being a carrier of having no alteration in the two copies of the SPOAN gene, being healthy and incapable of passing on the mutation. “One in every 250 of the Serrinha population has the illness and one in every nine is a heterozygote for this condition”, estimates the neurologist Fernando Kok, who carried out the clinical and neurological description of the SPOAN symptoms.

Trembling eyes - During the first months of life, the recently born attacked by the illness do not show any clinical symptom of SPOAN. They look healthy, just like any other baby. If it wasn’t for a small detail, perceptible only to those who have had a history of the illness in the family: the children show “trembling eyes”, to use a popular expression from Serrinha. These abnormal and involuntary movements of the ocular globe, resulting from the congenital atrophy of the optical nerve, reduce the field of vision of those effected. To this ocular malfunction the doctors have given the name of nystagmus. In the recently discovered syndrome, the problem does not get worse over time, but the patient’s vision, even with the use of glasses, is not the best. “They manage to see the fingers of a hand at a maximum distance of two meters”, comments neurologist Kok. Married to a half cousin from Serrinha, fifty seven



A family member with one of the 26 people affected by the syndrome: recessive illness

year old Maria Inês de Queiroz had six children, of whom three died while still babies and three are alive, two men with SPOAN, who for most of the day are looked after their healthy sister. The mother of the house remembers having seen the tremor in the eyes of one of her sons when he was four months old. “I knew then that he had the deficiency. His eyes moved upwards”, related the ex-open air market seller, who sold clothes and lived for a decade in the city of Sao Paulo. Her memories of life in the city are not of the best. “I spent ten years going from one doctor to the next. There was a pediatrician who told me that Marquinhos was healthy—and that I was the sick one”, recalls Maria Inês.

Marquinhos is the endearing name that family and friends use when referring to the youngest in the family, twenty-seven year-old Marcos Roberto, who, like his thirty-nine year-old older brother, Chiquinho, has SPOAN. Probably the doctors thought that Marquinhos was normal because the boy walked until he was ten years old. The only thing was that he walked with difficulty and his mother knew that, the same as Chiquinho, who had walked until he was six, he had the same problem as his brother. Similar stories are not rare among the Serrinha families who have relatives with the new syndrome. They are the rule and not the exception, among the people who have lived with the SPOAN sick. A progressive spastic paraparesis of the lower and upper limbs—difficult terms of the medical language that mean the continuous stiffening and weakening of the legs and arms—is one of the clinical signatures of the syndrome. Another is progressive lesions of the motor and sensorial neurons, damage that further diminishes body movements and reflexes.

Paradoxically, in spite of not managing to move the legs spontaneously, almost all of the patients react abruptly when they hear unexpected sounds: they produce involuntary contractions in the muscles of the lower limbs.

Some inhabitants of the town say that certain children who were affected

had already been born more or less “unsteady”; without a lot of firmness to sit up or even to crawl. But even these sick children generally more precociously fragile, manage to move themselves, on their own or supported, with falls and frequent knocks, until a certain age, in general around ten years of age. The paralysis normally reaches the arms a short time later, at the end of adolescence or around twenty years of age. “With time, the hands of the sick person, who had never been given any form of physiotherapy, end up being semi-closed, in a way that reminds one of claws”, explains the biologist Silvana Santos. “I had put on high heeled shoes to help Sarinha to walk”, remembers Maria Euda de Queiroz, known as Dona Loló, a sixty-seven-year-old widow whose husband, Francisco Assis de Queiroz, had been her “legitimate cousin” i.e. first cousin. “She walked almost without falling until she was eight years of age” When a child, the youngest daughter of Dona Loló, today 21 years of age, had walked balanced only on her toes, like a hesitant ballerina, and the use of the high heeled shoes had serves her as support.

To meet up with Dona Loló in the small Rio Grande de Norte town is easy. It’s enough to pass in front of her house, located at the side of an Evangelical church, almost at the exit of the town in the direction of Martins, the neighboring municipality from which Serrinha dos Pintos separated in 1993. She spends her afternoons there, sitting next to her daughters: Sara and Eda, both with SPOAN and in their wheel chairs; Tranquilina, her granddaughter who has psychiatric problems and, as a consequence, does not stay long in any one place; and Iza, the only one of her five daughters without health problems.

Sula, her first cousin who also had SPOAN, died of cerebral aneurism in 1999 when she was 46 years old. “My husband, who had two handicapped brothers, said that we were very unlucky”, explains Dona Loló, who had attended school until the old six grade level and knows how to read and write. Her father, José Firmino de Queiroz, married twice and had eighteen chil-

dren, three of them handicapped. “If I had known of the problem, I would have tried to forget Francisco and find somebody else”, says the zealous mother without much conviction. These days Dona Loló gets up at 5:30 in the morning to make breakfast and wash and cloth her sick daughters, who are always well looked after.



nd to give a “dose of diazepam” to Eda, the daughter with SPOAN, while she’s still fasting, who is in the most delicate condition and who awakens with tremors typical of the abstinence syndrome. At night, to induce sleep, Eda takes another dose of the tranquilizer and Sara, her first and only medicine of the day. Dona Loló guarantees that she herself had already given up this habit, although she did not deny that she returns to taking the tranquilizer on more difficult days. “The girls become nervous for any problem”, she explains. Nervous is an adjective often used by the families of the victims of SPOAN in order to describe the behavior of the sick. It’s impossible to know since when patients, families and other people in the town have been consuming medicines that are controlled. That the practice is of long standing and institutionalized, there is no doubt. “We have 345 people registered at the city hall to receive, through prescriptions, diazepam”, says the pedagogue and ex-community agent José Antonio Queiroz, today Serrinha’s municipal secretary of health. This is almost 10% of the local population. Some townsfolk say that the number of tranquilizer users is, at the minimum, double.

Queiroz, Fernandes and Dias family names — Situated in a region of mountains of modest size, with around 750 meters in altitude, Serrinha dos Pintos has a pleasant climate for a place that the maps locate in the interior of the Northeast Caatinga (shrubland) with an average temperature lower than 25°C. In spite of the almost 400 kilometers that separate it from Natal, the state capital, the town is of easy access. From the state capital one can arrive in this little known piece of Rio Grande do Norte by way of paved roads and potholes are

not a problem during the journey. At its beginning, some 200 years ago, when it was still a part of its neighbor Martins, Serrinha was no more than a large ranch. From the initial inhabitants of this extensive rural property, practically all of the current population are descendants with Queiroz, Fernandes and Dias in their surnames.

In Serrinha rain is not so scarce, the vegetation at this time of the year is abundant and the plants show hues of green normally not associated by the citizens of the south to a semi-arid area. This is a poor town, without a doubt. But its town center is clean and the streets are paved with stones. There are no signs of misery. Probably in the backland small farms the situation may well be more precarious. “We have eight public schools”, says the teacher Leidmar Fernandes de Queiroz, the town’s deputy mayor, Léia’s father, for those in family, Leinha, a twenty-year old girl with SPOAN and with a beautiful smile.

For the hospitalized and humble people of Serrinha, from whose houses one does not leave without having taken a cup of coffee or having tried a corn cake or piece of salted meat, the work that exists is agriculture, in general subsistence agriculture. They plant corn and beans and remove the nuts from the cashew tree. For the more learned or influential, there is the alternative of getting a job at the city hall. There are no banks in the town and the closest bank branch is in Martins. The pensions of the oldest citizens and the money coming from federal programs such as Family Grant (Bolsa Família), are also important sources of family income. In the majority of cases, those handicapped with SPOAN (and other pathologies) have been pensioned off and therefore also help to reinforce the household income. But the most of the city revenues do not come from some local economic activity. It comes from a federal grant known as the Municipalities Participation Fund, with an annual value that runs to about R\$ 2 million. In the 2003 registers of the National Traffic Department there are around 300 vehicles with the town’s number plate, and almost two thirds of them are motorcycles. More than transport animals and cars, the motorcycle stand out in the local countryside.

The mapped illness

The SPOAN syndrome was discovered in Serrinha dos Pintos, a town of 4,300 inhabitants situated 370 kilometers to the west of Natal



Since the end of last year, Serrinha has been able to count upon a hospital. Or better, can count and cannot count upon. The building of the Mista Tereziinha Maria de Jesus unit, planned to be a hybrid of hospital and health clinic, was ready in November last and is partially in operation. Formally, it is underused and the town doesn't have the money to make it work completely. The reason: built with federal cash contrived with the support of a Rio Grande de Norte politician of some influence in Brasilia, the establishment, according to the municipal secretary of health, José Antonio Queiroz, was conceived for a town of 20,000 inhabitants, five times greater than the local population. To sum it up, it's a lot of nuts for a small cashew tree like Serrinha. Almost all of its most sophisticated equipment such as the X-ray machine, are still in their boxes. The present electrical circuit for the building cannot support the equipment. The majority of the medical rooms are empty. "It's going to be difficult for us to make all of the hospital operational", the municipal secretary of health states frankly. One cannot say that a mixed unit does

not work because two general clinical doctors and two dentists provide service during the week in the ample sized building, also frequented by the personnel of the health clinic and by a cardiologist who fortnightly attends to the town's citizens. There are as well six hospital beds, two for men, two for women and two for children, which can house patients during the day, up until five o'clock in the afternoon. For consultations with other specialists, the townsfolk have to fall back on the services of the neighboring towns, or not even neighbors, as is the case of Natal. Every fortnight a van with patients sets out for the state capital.

Neighborly suggestion - Mixed up by laymen and doctors with other types of paraplegia and even with polio, the SPOAN syndrome was only identified thanks to the instincts of the scientist Silvana Santos. And a dose of good luck. It is possible to say that, in the first moment, it was the illness that found her and not the other way around. Afterwards she went looking for it. One of her neighbors in Butantã, a district in

São Paulo city, Zilândia Dias de Queiroz, a twenty-year-old young woman, was from Serrinha dos Pintos and had a different form of a physical handicap. The two of them became friends and the researcher began to make informal contact, as yet without any research project in mind, with the reality of the small town in Rio Grande de Norte. "She told me that there were other handicapped people in Serrinha and that there ever-yone was related and had married cousins", Silvana recalls. During 2001, at her own initiative, along with her two small daughters, the biologist went off to the interior of Rio Grande do Norte, on a journey that was a mixture of work and a family holiday. She was shocked with the quantity of consanguinity unions in the locality and the number of handicapped people. She returned convinced that in that location there was a lot to be researched.

Since then the biologist has visited Serrinha on three other occasions, the last one being last month, and became involved in the work with the sick of the town with a reasonably sized group of researchers from the Human Genome

Studies Center of USP. From the scientific point of view, the most visible result of this concentrated effort was the discovery that the form of Zilândia's physical handicap is, in truth, a new type of neurological disorder, named the SPOAN syndrome, which had not yet been described by science and should set off a chain of studies into the pathology. "Now we have to study, and urgently, these illnesses of consanguinity origin, which appear in small towns in the interior of Brazil", affirmed neurologist Fernando Kok. "Today these places are no longer isolated within the country, and, in a short time from now, it will no longer be possible to discover the origin of certain health problems." Numerous families, with many unions among related people, such as that of Serrinha, are becoming rarer and rarer.

In Brazil, it is estimated that 2% of the marriages occur between consan-

guineous couples. And it is exactly in this type of environment that new hereditary illnesses are found, such as SPOAN, or those involving genes of pathologies already known.



During the 90's, the researcher Maria Rita Passos-Bueno, also from the Human Genome Studies Center, discovered in two mutation genes associated to health problems when she had analyzed the DNA of the large family in Euclides da Cunha, a town in the state of Bahia of 55,000 inhabitants. One of the genetic alterations, identified in twelve individuals, had caused the Knobloch syndrome, a form of progressive blindness. The other, present in six patients, had led to a form of muscular dystrophy. "This town in Bahia was also founded based on a large ranch, just like Serrinha dos Pintos", says Maria Rita. As well as the excellent scientific

results, the research rendered practical dividends. Today there are predictive tests, developed at USP, capable of saying if the pregnant woman is carrying a baby with these two illnesses or if a couple runs the risk of having children with these problems. It is hoped that the same thing can shortly be achieved in the case of the SPOAN syndrome.

Whilst this does not occur, the mere presence of researchers in the heartland of Rio Grande de Norte, even though only occasionally, is serving as a stimulus for the local handicapped patients and their families to organize themselves. Almost a year ago the Association for the Physically Handicapped of Serrinha dos Pintos was founded, with a double room with a bathroom situated right in front of the prefecture. Almost 300 people, between the sick and the healthy, contribute monthly to the entity. The donations vary from R\$ 2 to R\$ 5. With the money collected, five wheelchairs with special wheels for the bath were purchased and a wheelchair

A "family problem"

If the researchers no longer have any doubts that the SPOAN syndrome is a recessive genetic disorder, inherited by some offspring of consanguineous marriages of Serrinha dos Pintos, the parents of the sick still do not think that way. They attribute the genesis of all of the cases of the syndrome to a "family problem"—to hypothetical hereditary syphilis that had attacked them some 150 years ago, a common antecedent, "old Maximiliano", and spread through their blood to their descendents. "My grandparents told me that the problem came from the Days of the Cattle Water Hole", tells sixty-five-year old Laurita Firmino de Queiroz, making reference to the family root that, sometimes, is pointed to as the depository of the origin of the physically handicapped. The parents of those affected by SPOAN also suggest that their children had only began to have greater difficulties of movement after having been the victim of some traumatic event in their childhood, such as a raging fever or measles. Dona Laurita remembered that her 43-year-old

son, Esdras, who has the syndrome, had a strong inflammation of the throat. "I grew and my body didn't accompany it", says the outspoken Esdras, attempting to explain his very own difficulty of movement. "I think I lost the practice of walking."

Based on common sense, the thesis that family blood could be the agent of the hereditary transmission of an illness such as SPOAN could be valid during the 19th century. At that time, serious researchers thought that way. Today, with the advance of science this idea can no longer be told, as science attributes the cause of the pathology to a genetic mutation. Nevertheless, this type of conception, abandoned by the academic world, still persists in the minds of many people, above all in a locality of simple people such as Serrinha. "One of our challenges is to explain to the town's population, in a simple manner, the significance of our research", explains the biologist Silvana Santos, who in August will launch a book with respect to how laypersons understand the concepts of genetic heritage. "The people need to understand the significance of being a heterozygote for an illness such as SPOAN and also which are the repercussions of the eventual development of a prenatal test capable of identifying, while still in the woman's womb, the babies that carry the syndrome."



The town has its economy based on corn, beans and the cashew nut, but the major part of the money comes from the Municipality Participation Fund

reformed. Although there is no lack of family relationships among the inhabitants and the place is small, Serrinha seems to be discovering its physically handicapped with SPOAN and other pathologies, only now. “It was only when I returned here did I see that there were so many physically handicapped in Serrinha”, admits Gilcivan Geraldo da Costa, a native of the town who became paraplegic in Sao Paulo on falling from a roof and now presides the physically handicapped association in his native land. “People only recognize the problem when they have the problem.” One of the entity’s most notable works was a survey about the number of physically handicapped in the municipality, which comes close to 140 people. That is to say, there are a lot more physically handicapped here than the 26 known victims with SPOAN. “There’re lots of people with mental problems, Down syndrome and deaf and dumb”, says Odi dos Santos de Queiroz, a volunteer in the entity that looked after this survey.

The association’s information matches up with the official data concerning Serrinha dos Pintos. On a list of 50 national municipalities with the largest percentage of physically or mentally handicapped people, the place where the new neurological illness was discovered occupies the 38th position. Almost 6% of its inhabitants show some form of deficiency. “There are

another six towns in Rio Grande do Norte within this ranking”, says the neurologist Fernando Kok, making reference to the municipalities of Riacho de Santana, Cruzeta, Timbaúba dos Batistas, Olho-d’Água do Borges, São Miguel and Pilões. The researchers also believe that there could well be cases of SPOAN undiagnosed — and of other illnesses — in these Rio Grande de Norte locations, which are neighbors of Serrinha dos Pintos. “In the immediate future, we need to concentrate on the studies with SPOAN in Serrinha and to attempt to improve the quality of life of those affected with the syndrome, especially the youngest, who could maintain good posture through adequate physiotherapy work”, suggests Silvana Santos. “But, shortly, we’ll have to look at the other towns.” And not only in the State of Rio Grande do Norte. Ten of the 50 municipalities with the highest number of physically handicapped in Brazil are located in Minas Gerais. •

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