

Yale CANCER
CENTER

answers

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Sickle Cell Disease

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week, Dr. Chagpar welcomes Dr. John Roberts for conversation about sickle cell disease.

Chagpar Let's start off by having you tell us a little bit about what you do and how long you have been at Yale?

Roberts I arrived to Yale in July, so I have only been on the ground for a couple of months. Previously I worked at Virginia Commonwealth University in Richmond and I really had two jobs there, one was that I was involved in medical oncology at the cancer center, but my other job was that I was co-director of the adult sickle cell program at Virginia Commonwealth University. I was in that role for about 15 years and in that role we developed a program to care for adults with sickle cell disease that attempted to address this problem on an outpatient basis, and also whenever patients were interacting with the health care system, when they were in the clinic, in the emergency room, or in the hospital. We also conducted research related to sickle disease and we conducted education programs both for trainees, health professional trainees like doctors and nurses, and also in the community. I was looking to relocate to New England and Yale was looking for a person who was interested in sickle cell disease and I am happy to be here in this role as director of the adult sickle cell program.

Chagpar Are you going to be trying to do pretty much what you did at Virginia Commonwealth University then?

Roberts Of course Yale-New Haven Hospital and Yale have a different environment than Richmond, but we thought we made some accomplishments in the program in Richmond, and in working with folks at Yale, I hope to have similar successes here in New Haven.

Chagpar That is really interesting. So sickle cell disease as I understand it is pretty rare, is it not?

Roberts It is a rare disease. Sickle cell disease in the United States affects almost exclusively African Americans. It is a genetic disease which means it is inherited and it is a disease that is inherited in a manner in which neither parent has the disease in most cases, but rather are carriers for the disease and it is only when two persons, a man and a woman, each of whom is a carrier of the gene for sickle cell disease have children, those children may be affected by sickle cell disease and then the odds are that one in four of their children will be affected by sickle cell disease. So, the child gets one gene for hemoglobin from each parent and there is a 50-50 chance that they will get the sickle cell gene from the mother and a 50-50 chance that they will get the sickle cell gene from the father, and so there is a one in four chance that the child of two adults with the gene for sickle cell

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disease will actually be affected by the disease. In terms of frequency in the United States, about one in four hundred African Americans carry the gene for sickle cell disease, but again these people do not have the disease, but if two people are having children together, and each of them is one of these carriers, then their children have a one in four chance of having sickle cell disease. Throughout the nation there are about 100,000 to 200,000 adults with sickle cell disease.

Chagpar Wow, and is there a regional variation in the country as to where sickle cell disease might be more prevalent?

Roberts There are going to be more people affected with sickle cell disease in areas of the country where there are more African Americans. I practiced for 10 years in Vermont and there were virtually no patients with sickle cell disease in Vermont, but in Richmond where African Americans are about a third of the population in the city and metropolitan area, we had about 300 patients who we cared for with sickle cell disease in Richmond. I think in the Yale-New Haven Hospital area there are probably about 150 adults with sickle cell disease. But Yale-New Haven Hospital sees people from beyond the Yale-New Haven area. I am new to Connecticut, as you know, but my impression is that adults with sickle cell disease are seen in New Haven, Hartford, Bridgeport, and probably some patients are seen in hospitals in New York City.

Chagpar Tell me a little bit more about sickle cell disease and what it means to a patient that might have it?

Roberts We used to call this disease sickle cell anemia, and anemia means low red blood cells in the blood, and red blood cells are the cells that carry the oxygen in the blood and people who are anemic suffer from a deficit of oxygen. If it is a longstanding problem they might be short of breath with exertion or be fatigued and not able to engage in normal continuous activity. If it is a sudden onset condition, if people are suddenly anemic, then they can have dramatic shortness of breath and realize that they are really sick and go to the hospital. And anemia is a hallmark of sickle cell disease, so adults with sickle cell disease have red blood cell levels that are only about two-thirds of the level seen in the rest of the population. On the other hand, we changed the name from anemia to sickle cell disease because anemia is just one of the manifestations of the disease. Other manifestations of the disease are pain, which unfortunately is a common problem in patients with sickle cell disease. It is not related to anemia directly, but it is a common problem in patients with sickle cell disease and these patients can have other problems effecting virtually any organ in the body including the brain, the lungs, the liver, the spleen, the kidneys, and the skin. It is a disease that people become aware of because of low blood counts or pain, but it is a disease which can affect the entire body.

Chagpar Given the fact that this is a fairly rare condition it sounds like it affects the whole individual. Tell me a little bit more about how you got interested in sickle cell disease because it sounds like you are very passionate about this particular field.

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Roberts

That is a good question. I should mention that it is a rare disease, but an important one and it is a disease that affects infants and babies. Actually the most common way persons are identified with sickle cell disease now is through neonatal screening. In Connecticut and in other states in the country, before a baby is discharged from the hospital they will have a blood sample taken, usually with a tiny pinprick in the heel and that blood sample is sent to a lab and the lab will look in the blood to see if there is evidence of sickle cell disease and a number of other genetic conditions. If there is evidence of sickle cell disease, then it is the responsibility of the pediatrician to contact the parents of that baby and inform them that there is concern that the child may have sickle cell disease. The test is not perfect and so other tests need to be done, but whereas in past years we often did not know people had sickle cell disease until they came to the hospital with the problem, now our goal, and we are largely successful, is identifying babies and children, infants with sickle cell disease before they ever have any problems and working closely with the parents to anticipate problems and trying to deal with them. Patients are doing much better with sickle cell disease now than they did only 20 or 30 years ago. Unfortunately, when I first began my training in medicine 35 years ago, it was uncommon for patients with sickle disease to live into adult life. With general medication advances over the past several decades though, most patients with sickle cell disease are living to be adults, although their lifespan is definitely shorter than that of the average Americans. Whereas in America the average lifespan is in the mid 70s, for persons with sickle cell disease the average life span is to live into their late 40s or early 50s, much too short. I was attracted to the problem of sickle cell disease because it is an area where we need better therapies and although I am a practicing physician, one of the things I am very interested in is developing new therapies. Specifically new drug treatments for diseases. The first projects I worked on related to sickle cell disease were drug development projects. Unfortunately, the projects that I worked on with other investigators at Virginia Commonwealth University were not successful. While we were working on those projects, other investigators at Virginia Commonwealth University were working on a national drug development project and it was demonstrated that hydroxyurea, which is a pill that previously had been used to take care of chronic leukemia, can be helpful in the treatment of people with sickle cell disease, and so now we think that most adults with sickle cell disease probably should be taking hydroxyurea therapy on an outpatient basis and we know that hydroxyurea therapy prolongs the life of patients with sickle cell disease, delays the onset of problems related to sickle cell disease, and prevents pain. That is the only drug, however, that we have which is specific for the treatment of sickle cell disease. Other diseases have many drugs, for infections we have a whole host of drugs, for cancer we have a whole host of drugs, but for sickle cell disease at this time we have one drug, hydroxyurea, and so one of my goals for the adult sickle cell program at Yale in the future is to be involved in research to develop better treatments for adults with sickle cell disease. I think there are going to be promising drugs coming down the pipeline, so to speak, from pharmaceutical companies and from research labs and I would like patients in New Haven to be able to have access to these promising new drugs as they first become available.

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Chagpar Can you tell us a little bit more about some of the research and some clinical trials that you are doing that might advance this, because it seems like it is a huge problem when you only have one drug? Tell me a bit more about that?

Roberts Well I just arrived and we do not have a research program ongoing at Yale, but I can describe some of the research programs I have been involved in in the past. I cared for patients who had been involved in the hydroxyurea study. That was a study that involved about 300 adults with sickle cell disease. It was conducted at 20 centers taking care of patients with sickle cell disease throughout the country and the results were first reported in about 1993 or 1994. It was a randomized placebo controlled trial, those are complicated words, but mean that half of the patients were treated with the drug we were testing and half of the patients were treated with a sugar pill. The patients knew when they enrolled in the study that they might get a sugar pill, but while they were actually participating in the study they did not know and actually their doctors did not know if they were getting the sugar pill or the drug. The reason we design the study that way is that when drugs have only a small affect on the disease, it may be a clinically important effect, but it may be a small effect. The best way to determine whether the drug is really working or not is to have a comparison group so we can see how the two different groups are doing and with this comparison group we were able to show that the patients getting the real drug did better than the patients getting the sugar pill. As soon as we had that information we stopped the study, we told the patients that the study was effective and we offered the real medicine to all the patients on the study. Not all drug development studies involve a sugar pill, or a placebo, but at some point in the development of many drugs that is an appropriate scientific approach to trying to study the drug. We did another study at Virginia Commonwealth University, a colleague of mine Dr. Wally Smith was the lead investigator in that study, and we had adults with sickle cell disease fill out a daily diary about their experience with regard to pain and the use of pain medications. They told us how much pain they were having, what part of the body was being involved with pain and what pain medications they were using and how effective those medications were. We had about 250 patients fill out diaries for about six months. We had about 25,000 daily patient diaries that we entered into our computer database. Whereas previously people had said the pain of sickle cell disease was something that came and went, what we learned in these diaries was that unfortunately for the average adult with sickle cell disease, these people experience pain most of the days of their lives. This was new information that we developed and in this gave use insight into, this is not a problem that we can only treat in the hospital, it is a problem that we need to be approaching in the clinic and managing on a daily basis throughout people's lives.

Chagpar It sounds like as time moves forward and you develop newer drugs and newer therapies that you are really going to be able to compare it to a drug that you already have that is effective and also use it in the clinic as well as in the inpatient setting.

Robert That is certainly the goal.

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Chagpar We are going to continue our conservation, but first we are going to take a break for a medical minute. Please stay tuned to learn more information about sickle cell disease with Dr. John Roberts.

Medical Minute

Breast cancer is the most common cancer in women. In Connecticut alone approximately 3,000 women will be diagnosed with breast cancer this year, but there is new hope. Earlier detection, non-invasive treatments, and novel therapies provide more options for patients to fight breast cancer. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection, and a healthy lifestyle breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatment available to patients. A potential breakthrough in treating chemotherapy resistant breast cancers is now being studied at Yale combining BSI 101 a PARP inhibitor with the chemotherapy drug irinotecan. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcast Network.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest Dr. John Roberts and we were discussing sickle cell disease, which is a fascinating problem. Dr. Roberts, you mentioned earlier that this is a disease primarily of African-Americans, tell me more about that and why this affects African Americans more than it affects Caucasians.

Roberts That's a very interesting question Anees, and we think we know the answer to that. People in Africa are exposed to malaria, it is a common cause of death in Africa and malaria is a disease of the red blood cells. It turns out that the people who carry one sickle cell gene in their body, have the so called sickle cell trait, are somewhat protected from the malaria infection and so we imagine that sometime in the ancestral past in Africa one or several individuals developed a spontaneous mutation in which one of their genes for hemoglobin in red blood cells the protein that carries oxygen, the mutation affected that gene in a way that when that person's red blood cells got infected by malaria insects, the cells actually die and the insects have no cells to grow in, so they cannot go through their lifecycle. So it actually protects people who are living in Africa from the problem of malaria, which is a very common problem in Africa, and that is why the gene persists in the population, but a side effect in a sense is that if two individuals who have this mutation, and most likely in Africa, at least a years ago, that would occur in cousins or distant cousins that would have a child together, then that child might inherit the sickle cell gene from both the mother and the father, and now the child has two sickle cell genes and their red blood cells not only are not a favorable place for malaria insects to grow, but they also do not do a good job of delivering oxygen throughout the body. The term sickle is related to a phenomenon that was discovered about sickle cell disease. Red blood cells are generally round or disc shaped cells, sort of like a Frisbee, but when the hemoglobin, which is the oxygen carrying substance in the red blood cell, is the so

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called sickle hemoglobin from this mutation, there is a chance that the hemoglobin within the cell may crystallize, just like salt crystallizes in a heavy salt solution, or sugar crystallizes in a heavy sugar solution, when the hemoglobin is crystallized in the blood cell, the cell can no longer carry oxygen and the cell, instead of being a flexible disc which travels through the blood vessels, becomes a rigid sickle shaped cell. This was actually first observed in African Americans living in America by a physician in Baltimore who was trying to understand why an African American patient of his had a low red blood cell count and they looked at the blood cells under the microscope and described these strange sickle looking cells. We think that these cells that are sickle shaped get tangled among themselves and as they try and travel through the tiny blood vessels, obstructions occur in the blood vessels and that leads to pain when the obstructions is in the joints, the bones or the muscle and leads to other sorts of problems. So sickle cell disease arose throughout mankind in Africa and it arose in Africa because the gene, if you just had one of the gene copies actually allowed you to do a better job living in an environment that was infested by malaria-infested mosquitoes. But it had the unfortunate consequence that if there are two genes in a person's body than they have the disease and the disease is a difficult disease. We have sickle cell disease in America then because of our tragic history of slavery in taking people from Africa in bondage and bringing them to America and some of those persons had the sickle cell gene and as they lived in America and their progeny have lived in America, the problem with sickle cell disease now affects African Americans.

Chagpar If this is a problem that started because of a mutation or a mistake in a gene, are there new therapies that are looking at maybe correcting the mistake in the gene?

Roberts Indeed, we have all been hearing about gene therapy for 2 or 3 decades now and yet the promise of gene therapy has not been realized yet, but sickle cell disease is an obvious candidate for gene therapy. We know the specific gene that causes the problem. We know where the gene is expressed in the human body; it is expressed in the blood cells, in the bone marrow that makes red blood cell. There is another gene in everybody's blood cells, the baby hemoglobin gene called the fetal hemoglobin gene, all of us when we are babies do not have the normal adult hemoglobin in our body. We have baby hemoglobin, and that is because of the relationship between the unborn baby and the mother and how to pass oxygen from the mother's circulation to the baby's circulation. It takes a special kind of hemoglobin called baby hemoglobin or fetal hemoglobin. That baby hemoglobin gene becomes silent, it is no longer activated in infants and children and adults and we all switch over to our adult hemoglobin gene, but in patients with sickle cell disease they do not have the normal adult hemoglobin gene, they have the sickle hemoglobin gene. So, if we could replace the bad gene in these patients, or even if we could get the now quiet baby hemoglobin gene to wake up and express itself again in adults, we could essentially cure sickle cell disease.

Chagpar Wow.

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- Roberts It is an obvious target for gene therapy, on the other hand, despite the fact that it has been an obvious target for gene therapy for 50 years now, we have not been successful at developing gene therapies for sickle cell disease. There are institutions doing gene therapy research throughout the country, and indeed Yale has an active gene therapy research program, so one of my hopes is that a cure for sickle cell disease will be discovered some place in the world in the next few years and there is even the possibility that it could be discovered at Yale through the Yale gene therapy program, but that is just a vision that is not happening tomorrow.
- Chagpar That is exciting, I mean, wouldn't that be great?
- Robert It would be wonderful if we could approach people with sickle cell disease and say, you are born with a genetic defect which we can fix and your life will be changed because of that. And that is I think a reasonable goal for medical progress and for all people in the United States, especially the African American population which bears the burden of this disease, and I certainly hope that it is realized in my lifetime.
- Chagpar Tell me about other exciting research visions that you have for the next five to ten years?
- Robert Well, even if we cannot accomplish a cure of sickle cell disease with gene therapy there is a hope that we can find drugs which will improve the life of patients with sickle cell disease. And one type of drug would be a drug, without doing a gene therapy per se, if we could wake up that baby hemoglobin gene in adults with sickle cell disease and get it to be active again then we could greatly improve the lives of patients with sickle cell disease, with something short of a gene therapy. There will be studies of new drugs which change the way the body deals with the genes and I am hopeful that myself and other investigators at Yale will be involved in clinical trials of these drugs in the future at Yale. A big problem in sickle cell disease is pain and we have medicines that are very effective for the treatment of pain, but our most effective medicines for the treatment of the pain are narcotics, and of course narcotics are always a double-edge sword because they can be tremendously helpful and very important for patients with painful conditions, but on the other hand for a subset of any population of any group of patients treated with narcotics, there is risk that there will be problems related with the narcotics. Problems of dependence, or tolerance or addiction and so another important area of research, which is ongoing, would be to identify drugs which are as effective as narcotics at controlling pain, but do not have the same risk or side effects of narcotics in terms of tolerance and dependence and addiction and that is another potential active area of research. Then some of the systems that sickle cell disease affects are the lungs, the liver and the kidneys, and so I anticipate a focus on the above research looking at other drugs, which cannot cure the disease or effect the disease throughout the body, but on the other hand can have a meaningful impact on the disease in a specific organ system like the lungs.
- Chagpar When you were telling us the story about how hydroxyurea, which is our only drug currently for sickle cell disease was first found, you were talking about clinical trials, so it sounds like for all of

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these exciting therapies that are on the horizon, that clinical trials are really going to be important, but for some patients clinical trials might be scary. Tell us a bit more about what exactly is a clinical trial? Should patients be scared about this? Why are they important to move the field forward?

Robert It is certainly true that when you bring up the topic of clinical trials that can be scary or threatening to patients and that is very understandable. Because the truth is when we first begin investigating new drugs in people we do not know what is going to happen and there are risks involved, and the people who assume those risks are the first patients that agree to be treated with those drugs. We do not go into clinical trials just on a whim. Clinical trials are closely regulated in this country by the Food and Drug Administration and before we can go into a clinical trial we need to have a good scientific basis for doing the study. For example, in the last ten years scientists have developed a so called sickle cell mouse. That is a mouse which can grow and can propagate we can have multiple generation of these mice, we can have the mice living in the laboratory for many generations and these mice look like they have sickle cell disease. If you look at their blood in the microscope you can see the sickle cells and they develop manifestations in the mouse similar to the manifestation of the sickle cell disease in human. So, before a new drug is tested in humans it is very likely that it will be tested in mice who have this genetic condition of sickle cell disease and before a new drug will be go into humans, I anticipate that the Food and Drug Administration wants to see evidence that the drug may show some positive effects in the mouse model and so we can test new drugs for their potential to treat sickle cell disease in test tubes and in the sickle cell mouse and we can use computers to model what might happen if we gave these drugs to humans. On the other hand, the only way we know what a substance is going to do in the human body is to introduce it to the human body and so I consider the patients who are willing to be involved in clinical trials real heroes because they are willing to take a risk in the hopes that they will get better and also they will help scientists discover new knowledge that may benefit people with similar diseases in the future. I have been involved in new drug development for sickle cell disease in the past and I hope to be involved in it in the future. I have also been involved in drug development for patients with cancer, and in the cancer field where we have had more successes in treatment of this disease with drugs, there are literally patients who are alive today because they were the first people to be treated with a new drug ten years ago, and there are always risks, but on the other hand, it is those pioneers who are willing to be involved in new drugs who may be the dramatic beneficiaries of a new treatment.

Dr. John Roberts is Director of the Sickle Cell Program at Smilow Cancer Hospital. If you have questions or would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.