The Rare Disease Gazette

Conversations with the world's experts in rare disease

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A Page of History
also available in Chinese
Editorial
by James A. Levine
MD, PhD, President, Fondation Ipsen
www.fondation-ipsen.org
Rare But Not Alone

The plight of patients with rare diseases is a critical unmet need of patients in healthcare. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal Science, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public. In 2021 these webinars focused on improving the detection of rare diseases. The Rare Disease Gazette is a magazine that broadcasts these discussions.

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Sean Sanders (host):
Hello, and welcome to this second installment of the New Science and Life webinar series on rare diseases. I am Sean Sanders, Director and Senior Editor for Custom Publishing at Science. In this nine part series, we will delve into a number of different aspects of this important topic of rare diseases. You can find the recording at sciencemag.org. The term rare disease is not entirely accurate since collectively rare diseases encompass approximately 7000 disorders, affecting about 300 million people globally. Our first webinar discussion was broad, but today we will be focusing in particular on the challenges of diagnosing rare diseases. Patients with rare diseases must often live with no accurate diagnosis.

A significant part of the problem is the lack of awareness amongst medical and scientific communities, but there are also obstacles put up by medical insurance companies and the broad failure of the public domain to appreciate the hurdles faced by patients with rare diseases. Living without a diagnosis can impact a patient’s physical, mental and emotional wellbeing, while receiving an accurate diagnosis can allow a patient and their family to move forward with a focus on managing future challenges. I am so pleased to have a fantastic panel of experts who can provide us with insights and explanations.

You can email feedback to webinar@aaas.org. Now I’d like to give our guests a chance to introduce themselves and I’d like to start with Dr. Kym Boycott.

Kym Boycott: My name is Dr. Kym Boycott. I am a clinical geneticist in Canada. I work in Ottawa. I am also a clinician scientist. So, I spend about half of my time in the clinic and half of my time in the research lab, and my focus both in the clinic and my research program is rare diseases.

Sean Sanders (host):
Next up, we have Dr. Bill Gahl.

William A. Gahl: Yes, I am a senior investigator at the National Human Genome Research Institute. And I studied rare diseases. And I am also the director of the NIH Undiagnosed Diseases Program, which is part of the NIH Undiagnosed Diseases network.

Sean Sanders (host):
Third is Jean-Louis Mandel. Welcome, Jean-Louis.

Jean-Louis Mandel: Hello, I am an MD, PhD. I started working on rare genetic disease on the molecular side in 1983, and I have been directing diagnostic lab for genetic disease until 2016. And I am currently president of the Foundation for Rare Disease, which is a French foundation.

Sean Sanders (host):
Thank you so much, Jean-Louis. And last but not least is Dr. Anne O’Donnell-Luria.

Anne O’Donnell-Luria: I am a clinical geneticist at Boston Children’s Hospital where I see children and adults with rare disease, but I spend a majority of my time actually working as the co-director of the Center for Mendelian Genomics at the Broad Institute, which is a large scale International Research Consortium that works to really find new disease genes and better improve our understanding of the variants that lead to genetic diagnoses.

Sean Sanders (host):
Fantastic. Thank you so much, Anne. In case some of our audience missed the first webinar, or are new to the subject, Bill, I am going to ask you if you can help us to understand how we define rare diseases.

William A. Gahl: In the United States, there is a definition of a rare disease as one that affects fewer than 200,000 individuals. In Europe, there is a definition of a rare disease as one that affects fewer than one in 2000 individuals. And there are different definitions around the world of a rare disease. And I think that those are political, or in a way, economic definitions. But I think clinicians and clinical geneticists understand rare diseases in different ways, depending upon how many of those individuals with that particular disorder they see.

Sean Sanders (host):
We were chatting via email earlier and Jean-Louis, you brought up an interesting point, which is, why do children appear to be disproportionately impacted by rare diseases? It seems like a lot of them are found in children, is there a reason for this?

Jean-Louis Mandel: Yeah, I guess medical genetics started really, mostly was children disease, pediatric disease. And there were a few adult onset disease like Huntington’s disease with a very specific presentation. But for a long time, it was a pediatric diseases. And also, generally, if children are affected early on, they will keep the disease all the time, while adult onset, they don’t show the disease until maybe 30, 40, sometimes 60. So, this is different and what is certain is that what is now more searching for genetic disease in adults, than when was doing it 10 or 20 years ago. So recently, there had been neurodegenerative disease that had been found to be rare, monogenic disease, but this is quite recent.

Sean Sanders (host):
Anne, let me come to you. I believe you treat children in in your work, so when do these diseases usually show up? When you start seeing symptoms in children.
Anne O'Donnell-Luria:
There is first the aspect of when the symptoms first appear and when they are recognized. For a lot of rare diseases, it takes a while of seeing doctors and looking for answers before it is realized that something more complicated or something rarer is going on that needs further investigation.

Jean-Louis Mandel:
I’d add, some start prenatally where something does not happen correctly. Other diseases will start early on, like Friedreich’s ataxia, for instance, between 7 and 12. Other diseases will start even later. So, there is no rule, it depends really on each disease. Each disease is specific.

William A. Gahl:
I’d point out, too, that many children who have genetic diseases don’t survive till adulthood, and that changes the number of children who have it compared to the number of adults.

Sean Sanders (host):
Looking at the flip side, are we missing rare diseases in adults, especially in the aged, Jean-Louis?

Jean-Louis Mandel:
Totally, because we still don’t know them all. Recently, a frequent form of neurological disease has been found because a gene was identified. Before, nobody really thought that it would be genetic. So, we are discovering novel, rare genetic disease, I would say every week.

Kym Boycott:
I actually see a lot of adults as well as children and prenatal genetics, and I would say for the adults that we see, sometimes they become lost in the system, because there are many things that can look like a rare genetic disease, but actually are caused by say, diabetes causing a nerve problem in the legs. That might look like a rare disease, for example, or it has a similar presentation to a rare disease. And so, the frontline providers aren’t really recognizing the diagnosis.

William A. Gahl:
Most geneticists, clinical geneticists, especially, are pediatricians, so they are aware of genetic disorders. And it is only now that We are coming to recognizing adult genetic diseases more, and having internists and specialists understand them.

Anne O’Donnell-Luria:
Anne, more broadly, what factors are most critical in the length of time to diagnosis, and why does diagnosis take so long? Is it always possible to diagnose?

Anne O’Donnell-Luria:
There is a lot of factors that go into this; I think of them almost as the barriers or gates you have to cross. The first challenge is recognizing that you should be thinking about something rare, and that is often working with your pediatrician and your internist and recognizing that something is going on that maybe needs another specialty level of consideration. And so, the next challenge is getting to the right doctor, whether that is the geneticist, a neurologist, cardiologist, depending on what the medical issues are. Doctors maybe have to think a little bit outside of the box, into the rare spectrum. We need a lot of collective knowledge to really understand and think about these conditions and realize that they are out there. And then you get to accessing genetic testing. Not all of these diseases are genetic, but a large proportion of them are. In many cases, these are things you can suspect clinically, but you need to send the appropriate testing. Next, we have to figure out how to interpret the testing. Just because we can sequence something does not mean We are going to recognize the genetic change that is causing the rare disease. And then the next step is figuring out what to do with that information.

Anne O’Donnell-Luria:
It is a very long and complicated process. And that can stretch from getting a doctor quickly, having comprehensive testing sent, and figuring something out really fast, or even just sending the right targeted test and getting an answer from the first step. Or it can take a number of years and seeing a number of doctors to figure things out.

Jean-Louis Mandel:
I would add, at the beginning and at the end, there are two issues. At the beginning, at least in France, maybe in the US too, is how the GP does not believe the parent and might say, “Oh, there is a language delay. But you know, this is just right now, and in two months it will be solved.” Or behavior manifestations, maybe there is something in the family or, the first thing that the doctor really believes is an objective symptom. That may take time for a disease with a slow beginning. This is the beginning to have a specialist believe that symptoms may be genetic. But at the end, also, there has been an extraordinary improvement in genetic diagnosis in the past 10 years. Often, I see families that say, “Yeah, but my son has been tested. There was a genetic test 10 years ago, and that was negative.” But that does not mean that if you redo it now, even if it was done five years ago, and depending on which test – it can be positive. A negative test can be a negative test for the type of assay, and the interpretation changes every month, every year. So, a negative diagnosis can become positive, because there is advances in knowledge.

William A. Gahl:
We certainly have experience with families that have a child who has a particular disorder, and they don’t know what the disorder is. And when this first comes to light, they pursue a diagnosis very aggressively, and sometimes for a year or two years or three years or so. But then they begin to accept the diagnosis, or the fact that there is no diagnosis, and they fall off and don’t pursue it for a while. And then sometimes five, 10 years later, or so, they see something on TV, or they read the paper or something, and they find out that genetics has really come a long way, and then there is a recrudescence of interest in that. We get a lot of families that have had that history of let us say, a hiatus in pursuit of a diagnosis. I am sure Kym; you and Anne and Jean-Louis have had the same experience.

Jean-Louis Mandel:
Totally.

Kym Boycott:
Yes. We have actually just looked at that, in participants who are engaging in our care for Canada Research Rare Disease Research pipeline looking for a diagnosis, we actually mapped out all of their investigations from prenatal all the way to their current age. And just exactly as Bill is describing, you see these focal areas of activity by a trigger investigation and a little bit happens. And then there is a quiet for a year or two, and then it happens again. And as Bill pointed out, for some families that are participating in some of our research programs, there is a quiet time for 20 years before they come back, because there is been some something new that is happened.

Anne O’Donnell-Luria:
Rare disease is an unusual field in that so much more is being learned all the time. If you are needing management of
your hypertension or high blood pressure, maybe there is a new medication every once in a while. But for the most part, the knowledge is what we have. But for rare diseases, there is over 200 new diseases described every year, the techniques we are using in diagnostics are actually still changing almost every year. We are able to recognize more of the variation that contributes to disease. It is a much faster moving field than a lot of other medical specialties. And some of that is just because for so long, we knew so little that now we are kind of starting to catch up and understand more.

Sean Sanders (host):
Let me maybe put this to Kym, how would patients or the families of patients know where to look? Where can they go for this type of information? Are there resources or is it just, as Bill said, happenstance that they come across a TV program or a news item?

Kym Boycott:
Yeah, I would say for our families, the patients and families in Canada, it is not so much that they are coming across it in the news or in the paper, I think most often it gets triggered by some sort of new aspect of their presentation or something that has happened in their life that makes whatever they were dealing with a little bit more challenging. They re-enter the system, and they get this fresh set of eyes in terms of where’s the best place for you to go. I also think that Google and the equivalent search engines have changed tremendously since I first finished training 15 years ago or so. People can put in symptoms and go to all sorts of resources, many from North America, which are supported by the NIH, and then many in Europe, which are supported by programs like Orphanet. They have access to all this information to really empower them to ask the right questions to their care providers.

Anne O’Donnell-Luria:
And because a lot of rare diseases run in families, I think you see a lot of that initial flurry of sending a lot of testing and thinking about it as they are planning for other children. And then after a while, they are often siblings, they are growing up, they are thinking about starting their own families, and sometimes it restarts that genetic search.

Sean Sanders (host):
I change track a little bit to talk about the importance of a rare disease diagnosis. And the first question I want to ask broadly, what does a diagnosis really mean to a patient? If there is no treatment available, is a diagnosis still important? Jean-Louis, why don’t we start with you on this question.

Jean-Louis Mandel:
Yes. I think it is indeed very important to be able to put a cause and a name to an illness. There is a lot of interest in diseases with intellectual disability and sometimes behavior problems or a neurological problem. Often parents have a child that does not behave well. And from the outside, they think this is a fault of the parents, that they are not educating the child. And so, having a cause and a name identified is a first thing that I have not done something wrong, like I drank a glass of wine when I was pregnant, could this be the cause? I think this is one thing and secondly, it means that there are people interested, there are doctors, professionals, researchers interested in that disease and they are working to try to make things better - to better care. The third thing is that it allows parents and children who are affected by a similar disease to meet other families with similar problems in association Facebook groups. It allows us to share information and to know that, “Okay, it is rare, but we are not the only one to be faced with this.”

Kym Boycott:
I think what we hear from our families is, especially within the Canadian system is about visibility, and what they describe as visibility within the system. This is not only within the healthcare system, but also within our social systems. Where we can not necessarily treat or reverse what has happened, the visibility in the social systems, such as school and community, allows them to have access to resources they would otherwise not have without that clear diagnosis. It literally is a tag of visibility. And families, quite rightly, recognize that their ability to navigate those systems is much better if there isn’t a diagnosis.

William A. Gahl:
People can think about what the prognosis might be, what does the future hold for them, that there is a possibility of treatment. As mentioned, being member of a community is incredibly important. There is the issue of trust and relationships with colleagues. For example, if you have an undiagnosed disease and you cannot name it, then there is a certain amount of suspicion associated with you really having that disease. We noticed that in some of our families and patients, their colleagues wonder why they are missing work, and even relatives and physicians wonder that. It is particularly difficult for patients to go to a physician to look for help, and to have the physician, first of all, not know what to do, feel inadequate, and awkward and sometimes not want to see that patient, because the physician feels awkward. And so, there is an incredible amount of solace associated with a diagnosis.

I’ll just mentioned, one man that I saw in his 60s who had some motor disease came from Cleveland, he was a police officer, he came with his loving wife. And I saw him just briefly on Monday, and then we got a diagnosis that he had ALS on Friday. When we told the wife, she hugged me, and she hardly knew me, and she hugged me when we gave her husband a death sentence. It meant so much to her and to her family to know how to proceed with the family’s life. It is incredibly important. (William A. Gahl)

Jean-Louis Mandel:
Another aspect is about recurrence risk. Are there possibilities that the same couple may have child affected by the same disease, or maybe the sister of the affected child, and who considers being pregnant, can she have also an affected baby with the same disease? So knowing whether there is a risk of recurrence in the family and sometimes the family at large is important. I have been doing a lot on Fragile X, and sometimes you have distant cousins that may be at risk of having severely intellectually disabled child because of the disease that was once diagnosed in a second cousin.
I think that we have to always remember or always have to remind people that diagnosis is a cornerstone of medicine. It is what we do. It is part of what we do. This is what doctors and physicians, and allied health providers do. We are all working towards diagnosis. It should be no different if you have a rare disease. (Kym Boycott)

Anne O’Donnell-Luria:
Psychological relief on its own adds a lot of empowerment for families. This fully justifies the need for a diagnosis and medical care. But there are families that are able to start support groups and build the communities and then they are able to think about therapeutics, build up research for their rare disease, but if they are not having a diagnosis and not being able to come together and share this knowledge, then that is a totally missed opportunity without having a diagnosis.

Sean Sanders (host):
Bill, let me come back to you with the next question related to this, and that is, what are the dangers of a misdiagnosis versus no diagnosis?

Sean Sanders (host):
How does the particular type of medical system in a country impact what we have just been talking about, the reaching a diagnosis or misdiagnosis and the level of testing? In the US, there seems to be a lot of testing for different diseases, doctors usually want to cover themselves, hospitals as well. In other countries like Canada, I am not sure it is quite the same.

William A. Gahl:
Many people think that the United States system is provincial as well, but probably in a different sense. I would say two things. One is that for rare diseases, it is pretty much true that you have to go to a university-based center. I would ask Anne if she would confirm that or not, or deny that, but universities, medical centers have experts, and do research, and have funding for this, and are often associated with advocacy groups, and so they have the knowledge base and the expertise. There is a referral system that starts with a primary care physician and goes up to a university-based system. And the other is that for rare diseases, who know about diagnosis.

Kym Boycott:
I think there is some good European data, and we have some Canadian data, that looks at the number of missed diagnoses that families experienced on their diagnostic journey, which some people refer to as a diagnostic odyssey, because it is a bit chaotic. EURORDIS, which is the large patient organization, or umbrella for patient organizations in Europe, and the Canadian Organization For Rare Disorders, came up with numbers of: 3-to-11 missed diagnoses along the way. There can be all kinds of reasons for that, and this may have been suggested as a possibility, or the clinical presentation evolves over time, or it is just plain wrong. And every time that happens, you have delayed that diagnostic journey to its ultimate end point, which should be the correct diagnosis. It just further confounds what we are talking about: to cause harm, because of all of the other things that might be done in the spirit of that initially incorrect diagnosis.

Kym Boycott:
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again. And that is why it takes so long, at least in the United States, for patients with rare diseases to finally reach a diagnosis.

Anne O'Donnell-Luria: Insurance empowers a lot of families to get testing, but there are some insuranc-es that won't cover genetic testing, while there is not really a good way to tell. It is not necessarily how good your insurance is; it is just what their policies are about genetic testing. It is confusing for families. It is actually really confusing for doctors. A lot of doctors are probably not sending as much genetic testing as they would like to, because it is complicated for them to figure out how to access it. And that is another reason why it tends to be more academic centers that have a little more support, see patients, that they more frequently be interested in or want-ing to send genetic testing that they get a little more savvy on the systems. And there are a lot of patients that I see that I have a strong, strong suspicion that they have a Mendelian rare disease caused by a genetic condition that we should be able to diagnose by genetic testing, and I just cannot get the testing covered.

I am in a privileged position, in that I am connected to a lot of research studies, and at Boston Children's Hospital, we in general, have connections to research studies, so we refer them over there. And that is an option that many families choose to enroll in research and to ac-cess genetic testing that way. We have one called the Rare Genomes Project that works with any families anywhere across the US that is really trying to get away from the geographic model of having to come to an academic center and be able to work with families locally in their com-munities with their own physicians. But still getting that access has still been really challenging. There is a huge difference in access based on where you live and what doctors you see, and that is a problem.

Jean-Louis Mandel: Sometimes things that would look very good, are not. For instance, in France, there is a very good genetic test, which is called an exome. If you, do it in an ac-ademic lab, you don’t pay for it, so that is very good. But the problem is that these academic labs are not funded enough to do as many exomes as they would wish. So, what was a good thing, in terms of you don’t have to pay for it, means that you may have to wait for it, because there is not enough funding to do as many tests that would be needed.

Kym Boycott: The pandemic has taught us, with respect to access, is how much we can actually do by virtual care. And that has been a re-markable experience over the last year in terms of how to deliver genetics virtually. And it has allowed us to see our patients and families in areas such as Baffin Island, which my center looks after, by having them go to their closest nursing station and they can see me there. There is a nurse there to do measurements, we can take photographs, we can do almost ev-erything from there, take blood samples, and they never have to take the big, long flight down to see us in Ottawa. And if it is the wintertime, they actually, don’t then have to take the big, long flight, which is a whole thing when there is snowstorms and things like that.

Sean Sanders (host): The pandemic has clearly impacted our work in many ways that things are going to be very different going for ward and hopefully, in many positive ways. But before we move off this topic, there is one other piece that I wanted to touch on and that is newborn screen-ing. My understanding is that different countries do it differently. They test for different diseases, and even I think in the US within different states, they use different tests. So, Anne, can you outline the importance of neonatal screening and maybe where some of the challenges or deficits are?

Anne O'Donnell-Luria: In Massachusetts, we screen for about 60 conditions. It is a heel prick that is done on every baby that is born and a few drops of blood are transferred to a card that is been sent to the state lab that does a number of different tests all on these few drops of blood that are collected from each newborn. From this, we can find out information about the risk of developing a condition that is treatable, we can figure this out within the first few days of a ba-by’s life. There are some conditions where this provides helpful information, and you would refer them to doctors and you can ameliorate the course, and there are some that are babies that would actually present in a few days or around the time we get the result, very sick. And so having that information and knowing about the treatments you need to implement them are really powerful. It is only for about 60 conditions; focused right now on things that are treatable, but it is also focused on things that we can detect from the types of testing that we do, which largely aren’t genetic, which are largely metabolic or en-zyme assays on the blood spots. I think there is a lot more potential to expand this. This is what we are doing right now in Massachusetts.

William A. Gahl: In the United States, the states decide, because the state legislatures are pay-ing for it. Most of the diseases that are screened in the newborn period are rare diseases. But the most common one is hyperthyroidism, and that has an enor-mous impact upon people. The screen-ing is done by a procedure called mass spectrometry. And that may be changing slowly into a molecular screen, but there are issues with molecular screens. I’d say detecting people who have only one, allele mutated in a recessive disorder. In other words, you could call this a molec-u lar screen, first screen, one that might have a lot of false positives that have to be pursued. But there are false positives with the mass spec analysis now, too. Anyway, things are evolving, and newborn screen-ing is spectacular in terms of its effect upon the lives of people who are detected and can be treated early.

Jean-Louis Mandel: Maybe what one can add is that some diseases that are not so rare, that until a couple of years ago, were not on the agenda of neonatal screening, like very severe muscle disease, and spinal amyt-rophy. Suddenly these diseases become targets because there is an efficient treat-ment. But the treatment is only efficient if it is administered very early in the first weeks of the life of the child. Nobody was considering doing neonatal screening of spinal amyotrophy two or three years ago, but things have changed because you have efficient treatment that requires a very early diagnosis.

Sean Sanders (host): I am going to come to you, Kym, with this one last question in this topic area on the importance of diagnosis, and that is the role of genetic counseling in the diagnostic journey. Now that a lot more DNA testing is being done and it is a lot broader, we are testing full exomes. We are even looking at full ge-nome sometimes. Where does the genetic counselor play a role?
Kym Boycott:
Possibly in two places, probably. It may evolve over time, but definitely for the pretest counseling and post-test counseling and support. Pretest counseling, I think, is particularly important for those genetic tests that have some pretty serious implications about future health, it may be predictive in nature, may be uncertain in nature, may have other things tied to it like potential for discrimination and things like that. I think that is where it is important for genetic counseling itself to have a major role. With the post-test counseling — results — I think it is still really important to have an actual human involved in that process. Many of us are probably aware that there are a lot of companies that do testing, and you get some sort of online type of genetic counseling and that sort of thing. But that really just contributes, I think, to the accessibility issues for families. A big part of that post-test counseling is around education and empowerment. To make that fair for all, it really needs to be done by somebody who can connect with that patient and family on an individual basis and meet the needs that they actually have.

William A. Gahl:
And one way to look at it is if we have 23,000 genes, and there are maybe 8000 known diseases, we only have a portion of those, maybe 4000 or 5000 or that have been defined. So we have to define new diseases, and we have to, let us say, train and educate our physicians in detection of rare diseases and in pursuit of new diseases. And then the public has to recognize how to proceed if they have a family member or they themselves have something that is undiagnosed. And that involves a certain sequence of going to one physician then another physician then university physician, then maybe some center like the centers that Kym and Anne and Jean-Louis conduct.

Jean-Louis Mandel:
Maybe there is a limitation - maybe there are some diseases that we will never be able to put a name to because there is not a single gene as a cause. The disease may be an interaction between two or three different genes, and it is very, very difficult to sort this out, or an interaction of gene with environment. A classic disease when I was a young medical student was called G6PD deficiency, where you would start to be very sick if you ate fava beans. Because this was a disease that was quite frequent in Mediterranean countries, it was recognized. But imagine a disease where you have this interaction between the environment and the genetic predisposition, it may be very difficult. And we need a lot of research before we can diagnose more and more of these more complex diseases.

Kym Boycott:
I would reiterate that. We have mentioned that exome sequencing came along 10 years ago, and we are still talking about accessibility for patients and access. It is remarkable in terms of the rare diseases exome sequencing can help to diagnose. Exome sequencing still has great potential; it is still on an upward curve. New technologies that many of us on this webinar work on are going to need to come back in, by the same process that exomes have finally come in and these techniques will need to become accessible to patients because exomes cannot do everything. There are some disease mechanisms that are just beyond its reach.

Anne O'Donnell-Luria:
There is still a lot within the exome that we all agree that we need to find. There is still in the scientific literature about 200 new disease gene associations every year. But the other side of that is a lot of the ways we figure out these new links are by looking not just at the exome data (sequencing all the genes in patients with rare disease), but by comparing it to the genetic variation we see in billions of people on this planet. This gives us a sense of what kind of variation do we not see in the general population that does not have rare disease. Actually, there are thousands of genes that we see depletion for disruptive variation in the general population. There are candidate disease genes, but we don’t know the phenotypes yet. And so there just needs to be more access to sequencing. And these reference databases that we use, like the Genome Aggregation Database, need to grow, and we need to get more data into them. There are a lot of efforts to do that; this will empower a lot of discovery.

William A. Gahl:
We often get clues from animals or organisms that have mutations in some of those genes. There is sometimes incredible emphasis on next generation sequencing, which means exome sequencing or genome sequencing, but we should not forget about how important it is for physicians to talk to each other over a particular patient and share information, share their expertise. Just being over the bed of a patient or even outside of the hall and talking about the particular disorder and its manifestations is important. Someone might say, “Well, have you thought of such and such.” These interactions are incredibly important for making a diagnosis of a rare disease and even for the discovery of new diseases.

Kym Boycott:
One of the big challenges we are facing, as exome and genome sequencing are coming into the clinic, and being reimbursed by healthcare systems, there is the natural tendency to silo that data and not share it, as we have done previously in the past with research endeavors like Bill's...
Undiagnosed Disease Program and Centers for Mendelian Genomics. When patients and families are enrolled in research, they are looking for answers and they are keen to share with whomever can help them find that answer. But in the healthcare system, that culture of sharing is not quite as strong yet, and it really does need to be for rare disease. And so, at least in Canada, we are trying to push that agenda. How do we share between different healthcare custodians, essentially data custodians, such that we can make the test better for everybody? And that is really, really critical, especially in countries like Canada, where our population is lower. One center is not going to do hundreds of thousands of these things by themselves, we have to be able to share amongst ourselves for sure.

Jean-Louis Mandel:
Because of some diseases are extremely rare, we need sharing at the international level. There are already international databases, but there is not enough information in them. So I think there should be an international policy to try to have more sharing at the international level, because you need numbers. If a disease is very, very rare or a variant is very rare, you need to know about the 10 people in the world that are sharing the gene: are they affected or not? We need to push for this international cooperation. That would include details about the phenotype - the clinical manifestation of the patient. When you just have a database where you identify some people with this particular variant, but you don’t know their medical manifestations, you cannot interpret it. We really need much more of these databases.

Anne O’Donnell-Luria:
As we get into these ultra-rare conditions, there will be conditions that are currently only affecting 10 to 50 people in the world. If you think of how many countries we have in the world, there is no way these are going to be identified without having better integration of the data. We can do this in ways that are safe with data security and regulations to make sure that the data are used responsibly by scientists and physicians and that there are protections against identifying patients and confidential matters like that. There is a lot of work that needs to be done, but this is work that the community is able to do.

Kym Boycott:
The advantage of our Baffin Island experience and also where we call the Near North is that we approach this problem with virtual care. We have great experience on how to deliver virtual care pretty effectively. But the key component and why it works is that the people there are covered by healthcare, and they are covered with the same healthcare as somebody who lives in the urban center. Just because they are rural does not mean they don’t get the same test. So that has made this a much easier problem to try and tackle in Canada. It would be very different if there were marginalized groups that do not have access to healthcare or, an insurance plan that covers genetic testing. That is a bigger challenge.

Kym Boycott:
In developing countries, how do you begin to help in that situation where rare diseases probably are not the biggest priority? People in developing countries have things like infectious diseases and water quality and food access, to focus on. There are a number of international bodies like the International Rare Diseases Research Consortium and the Global Commission to end the Diagnostic Odyssey For Children, for example, who really have started to tackle and brainstorm the challenges in developing countries. And I think in the end, it boils down to a mentorship program with scientists like ourselves and colleagues who are able to support those countries that are making that transition, to be able to help their families with rare diseases get answers.

William A. Gahl:
And sometimes a champion is needed. The champion can be either inside or outside of that community. In the Undiagnosed Diseases network, international organization, there is now a developing nations working group that is pursuing the access within low and middle income countries for diagnostics and even treatment for rare and undiagnosed diseases.

Jean-Louis Mandel:
I would like to point out one issue about diagnosis; having the proper diagnosis is not the end of what the patient or parents are looking for. And often, because of exome sequencing, you find the mutation and say, “Your child has this very important neurological disease or intellectual disability because of a mutation in DYRK1A.” Okay, so at least they have the name, and cause of the illness. But then very soon, they will say something like, “Okay, what does it mean for the child? When will he age? What will he start to have epilepsys? Will this be something that gets worse? Will he get worse with time or will he stabilize or can he improve, can he start to speak, etcetera?” And all this information you need for each of the 5000-7000 of rare diseases. For each you need to know the natural history and the comorbidities. For instance, if the child with a neurological disease has digestive problem, is it part of the disease or just by chance?

It is very important that this is done internationally. We need to have the sharing of data on the medical history and as patients age so that we can tell parents what they have to prepare for. This is something that is needed, after diagnosis.

Sean Sanders (host):
I wanted to come to one last question. What should the general public know about rare diseases so that they can be better advocates for patients and families?

Anne O’Donnell-Luria:
When we talk about how, individually, these conditions are so rare, there are so many of them that in aggregate, you all have friends or possibly family members who have rare disease, and so being there for them. It is a hard thing to have something that is so rare that doctors, school systems and families may not understand. Being a good community member and asking questions is important. Individuals with a diagnosed rare disease become experts on their rare disease. Not everyone wants to talk about it, but for those that do; be there for them, and for those seeking answers. Share the message that we have learned a lot more. Keep talking to your doctors and other healthcare workers. Keep searching there is a lot more to be found.
Jean-Louis Mandel:
I think that the most important thing is for General Practitioners to learn about rare disease. They should not know about all the rare diseases, but they should have this question, for a child that a parent notices is not typical; “Could it be a rare disease? Could it be a genetic disease?” Because this is the way to next involve more specialized teams.

Kym Boycott:
I think that public support for research into rare diseases is important because we are still learning so much more about rare disease. The public should recognize that in-sights we get into rare disease, oftentimes help us with common diseases. Scientific advancement in rare diseases actually give us a really important insight into some of the really big common problems that are faced by many and there have been successes to show this.

Jean-Louis Mandel:
Messenger RNA vaccines were actually developed from a technology that a company thought could be applicable for rare disease. They saw the opportunity to use the strategy to rapidly develop vaccines for COVID-19.

William A. Gahl:
I would also suggest that someone or a family with rare disease keep medical records assiduously. Those are incredibly important, and not just the written medical records, but also the discs of the images and access to pathology slides if there have been biopsies. Also, keep reading and recognize that there is a sequence of events to go through — first, your general practitioner, then specialists, and then university-based researchers — in pursuit of the diagnosis of a rare undiagnosed disease.

Sean Sanders (host):
If you would like to send us your thoughts on this webinar, please email webinar@aaas.org. Thank you once again to our fantastic panel and to Foundation Ipsen for enabling this conversation through their kind sponsorship. Goodbye everyone and thanks.

Journal Club

Article of the month

It’s free at: https://www.mdpi.com/2073-4409/10/2/240?type=check_up_date&version=1

Take home:
1. Every part of the human body is made up of different types of cells such as, muscle cells, heart cells, brain cells and so on. Stem cells are baby cells that have not decided what cells they will become.
2. Under the right conditions stem cells can grow into muscle cells, heart cells or brain cells, or even can repair damaged tissues.
3. Many researchers believe the stem cells could help treat serious illnesses such as rare diseases, diabetes and Alzheimer’s.
4. One of the great challenges has been to get stem cells to the right body part. One delivery system – like Uber Eats – is to use tiny delivery vehicles inside the body - these are called ExtraCellular Vesicles (ECV’s not SUV’s!).
5. This week’s fantastic article is about stem cell treatments and ExtraCellular Vesicles. It explains how stem cell treatment may soon help millions of people.

A Page of History

Story of the month
The history of acromegaly
by Florian Delval

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Hello everyone, today we are going to talk about the history of a rare disease: Acromegaly.

As a reminder, in Europe, a disease is considered rare when it affects one person in 2,000. In the United States, a disease is considered rare when it affects less than 200,000 people throughout the country. As far as acromegaly is concerned, it is estimated that it affects between one person in 15,000 and one person in 25,000. Although it occurs most often between the ages of 30 and 40, the disease can develop at any age. Acromegaly is therefore characterized in patients in two different ways: an exaggerated growth of the face and extremities when it occurs after puberty, and a large waist when it occurs before puberty. In this second case, it has often been called “gigantism” throughout history. As we shall see in this regard, it took centuries for scientists to understand that acromegaly and gigantism were in fact the same condition. Today, we know that this disease is linked to an excessive production of growth hormone, called GH. According to the French portal for rare diseases and orphan drugs Orphanet:

“This hormone is a kind of messenger that circulates in the bloodstream and thus acts on the whole body. As its name suggests, it plays a major role in the growth of children and adolescents. However, it is also essential for adults, since it maintains the thickness of the skin and muscles and helps to reduce fat mass. Growth hormone is produced by the pituitary gland, a small gland the size of a chickpea, located in the brain. Acromegaly is most often linked to the “enlargement” of the pituitary gland, whose cells multiply and produce too much growth hormone. In fact, this enlargement is due to the appearance of a benign tumor, i.e. a non-cancerous mass in the pituitary gland. This tumor is called pituitary adenoma.”
The physical changes associated with acromegaly are slow and progressive, which often explains why patients often wait up to ten years before going to see a doctor and being diagnosed. The consequences of the disease can include back and joint pain, bone deformities such as scoliosis or protrusion of the sternum. In 40-50% of patients, a carpal tunnel syndrome also occurs, resulting in a loss of volume in the muscles of the hand. There are many other symptoms such as the development of the hair system, the increase in volume of certain muscles and organs such as the liver, thyroid and especially the heart. Diabetest and high blood pressure are also among other symptoms. As we will see in this episode, it is possible to find and imagine traces of acromegaly during antiquity. From the modern period onwards, the disease began to be described precisely until the Frenchman Pierre Marie gave it the name ‘acromegaly’ in 1886.

**Traces of acromegaly in ancient texts and in antiquity?**

We begin the history of acromegaly between myth and reality. We all know the story of David and Goliath, a story that characterizes the triumph of the underdog. Although the historicity of these two biblical characters is, quite rightly, subject to debate, it is possible to imagine that Goliath may have suffered from acromegaly. In chapter 17 of the First Book of Samuel, we are told that the Philistines are at war with the people of Israel. The two armies are facing each other, each occupying the heights of a mountain facing the other. Only a valley separates them. As it was common at the time, since this avoided a pitched battle between two armies and thus a bloodbath, the Philistines sent their best warrior, Goliath, to fight a Jewish warrior. The outcome of this duel would decide who would win the war. For 40 days, Goliath presented himself twice a day, in the morning and in the evening, in front of the opposing army, without anyone daring to go and challenge him in one-on-one combat. The text tells us that “at the sight of this man, all the Israelites fled and were filled with fear.” It must be said that the Philistine warrior was intimidating. He was tall, very tall... He was also massive, strong, and had an incredibly robust appearance. According to the biblical text, he would have a height of "six cubits and a span", or about 2.70 m. He worn cop-

Another example, this one a little easier to prove from a historical point of view, is that of Pharaoh Sa-Nakht. In 1901, a skeleton was found in the sumptuous Mastaba K2 tomb near Beit Khalaf, Egypt. It is estimated that these remains date from the 3rd dynasty, approximately 2700 BC. The remains are those of a very tall man for the time as he would have measured 1m87. 1m87 might not seem tall for us who live in the 21st century, but it is important to point out that the size of the different human populations has varied over the millennia. At the time, the average size of the Egyptians was between 1m60 and 1m70. These remains were therefore attributed to King Sa-Nakht, who was a king/ pharaoh of the third dynasty. This case is of great value as it could be the oldest known case of acromegaly. By comparing research papers, databases and photographs of Sa-Nakht’s skull, five scientists concluded in 2017, in a study published in The Lancet, that:

“Sa-Nakht probably had gigantism and is thus the oldest known paleopathological case in the world. Evaluation of the facial structure suggests a slight acromegaly, which could indicate a regression of hyperpituitarism. In ancient times, no surgical or medicinal treatment was available; therefore, regression could only result from degeneration of the pituitary gland.”

It seems important to specify that the remains of this man might not be those of Pharaoh Sa-Nakht. They could have been those of one of the members of his entourage. In any case, the splendor of the tomb indicates that in ancient Egypt, gigantism was not a factor of exclusion or social marginalization, which will not always be the case, as you will see, during these last centuries.

**Towards the understanding of the disease: the first descriptions**

Let’s take a huge leap forward in time and go directly to the 16th century in the Duchy of Brabant, which at that time was part of the Spanish Netherlands. It was the home of a brilliant doctor, Johannes Wier. It is to him that we owe one of the first medical reports of acromegaly. In the course of the centuries, these descriptions were based on patients themselves. In the case of
diseases such as acromegaly, the physical peculiarities that accompany the condition were the subject of curiosity, often misplaced by the public and the scientific community. In the case of Johannes Wier, it was his encounter with a woman of “gigantic” stature, who earned her living by travelling through many regions to exhibit her physique, that prompted him to seek out more details about her. In his treatise Medicarum Observationum, published in 1567, Wier explained:

“I inquired with specific questions and learned from her answers and those of her mother that she was born of parents who were both small and that neither of her ancestors was taller than the average man. From birth to her twelfth year, she was small; but by the time she had reached her fourteenth year and had been menstruating for some time, it suddenly stopped, and she began to increase in size, all her limbs formed proportionally so that nothing seemed unusual. Unless I am mistaken, when I saw her, she was in her twenty-fifth year from the time she noticed the cessation of her menstruation.”

Without knowing exactly what the disease was, and without even knowing whether it was actually an illness, Johannes Wier was putting his finger on something fundamental. For acromegaly sufferers, a reduction in the level of sex hormones can be responsible for the absence of menstruation or amenorrhea in women.

Two hundred years later, it was the French physician and surgeon Nicolas Saucerotte who described the case of a 39-year-old man who most likely suffered from acromegaly. In 1772, in a communication to the French Academy of Surgery entitled Singular increase in bone size of a 39-year-old man, he reported a progressive increase in bone and cranial circumference, prognathism, hypertrophy of the hands and feet and significant and generalized joint pain. It is difficult not to think of acromegaly, with the hindsight that is ours. In this communication, Saucerotte noted, but did not attempt to determine the cause of this “singular increase”. At the turn of the 18th and 19th centuries, this disease began to be recognized, without knowing what caused it. Several names were then attributed to it. In 1822, the French dermatologist Jean-Louis-Maric Albert gave it the name “Scrofula Giant Syndrome”. In 1864, the Italian neurologist Andrea Verga gave it the name “Prospopo-ectasia”, which translates as enlargement of the face. A little like Johannes Wier, 300 years before, Verga met a woman, somewhat by chance, suffering from acromegaly. He described this encounter in a publication entitled Singular case of prosopoectasis, published in 1864:

“Since 1860, visiting the chronically ill admitted to the church of Santa Maria ai Nuovi Sepolcri, I had been impressed by the sight of a patient [Maria B., born in Milan], whose waxy pallor and disproportionate size of the face were almost frightening. The staff who worked in this hospital must have been equally impressed, because they had nicknamed this woman “Big Face”. Seeing me looking at her, she told me that she had not always been ugly and that she used to look like other girls.”

Beyond these misplaced comments on the physical appearance of this woman, unfortunately typical of the time, Verga’s meeting with Maria B. was preponderant in the understanding of the disease. Verga continued to hear from the patient until her death two years later from the causes of typhus. He then asked for a post-mortem examination. During this examination, he found a walnut-sized tumor, which had caused a displacement of the optic nerves. He did not find the pituitary gland, however, and wondered whether it had disappeared or whether the tumor itself was a degeneration of this gland. Andrea Verga was not able to provide answers to his questions, but he did find something fundamental. 15 years later, in 1877, the French physician Henri Henrot made the same observation. While performing an autopsy on a patient with what was then still called “gigantism”, he found a tumor in the same place as Verga. In the same year, 1877, the Italian doctor Vincenzo Brigidi made exactly the same observation when he performed an autopsy on an actor suffering from gigantism. He was also the first to examine this tumor of the pituitary gland under a microscope.

The year was 1886 and this is how Pierre Marie described the first patient, aged 37:

“It was at the age of twenty-four, when her period suddenly stopped, that she noticed the sudden increase in her hands. At that time, her face also underwent changes ... so that when the patient went home, none of her relatives could recognize her. The whole feet are large, including the toes. Although the toes have increased in size, they have retained their shape, there is no real deformity, their appearance is simply that of a very tall person ... The tongue is enlarged ... The sight is also defective ... The top of the skull is almost the same size as the end of the chin. The lower jaw is well developed.”

With regard to the second patient, aged 54, Pierre Marie noted that: “the edges of the eye sockets are very thick, as well as the frontal eminences [...] The nose is large. The lower jaw is very thick.” He went on to suggest that this condition be called “acromegaly”. He explained:

“A state characterized by hypertrophy of the hands, feet and face which we propose to call, “acromegaly” which means hypertrophy of the extremities. In reality, the extremities are swollen during the course of the disease and their increase in volume is the most characteristic feature of this disease.”

Having examined these two patients while they were still alive, Pierre Marie did not refer to the pituitary gland. In that year, 1886, our French doctor was unaware of the discoveries of his predecessors on this specific point. It was finally the Lithuanian physician Oskar Minkowski who confirmed, in 1887, that enlargement of the pituitary gland appears in all post-mortem studies of acromegaly patients. At that time, however, a major question remained unanswered. Are acromegaly and gigantism two different conditions, or are they two forms of the same disease? For Pierre Marie and his collaborators, it was the first option. As Wouter de Herder tells us in a publication entitled History of Acromegaly, published in 2014, “gigantism was considered an exaggerated variant of normal development, while acromegaly was considered a pathological condition”. But this assumption would not hold for long. Only a few years later, in 1891, the Scottish physician Daniel John Cunningham, leaned in favor of two forms of the same disease. To arrive at this conclusion, he studied the skeleton of an Irish man who lived in the 19th century, called Jean-Martin Charcot, Pierre Marie met two patients suffering from acromegaly at the Pitié-Salpêtrière, at the request of his mentor.

Pierre Marie and the clinical description of the disease

All these discoveries and findings paved the way for the French physician Pierre Marie. A pupil, disciple and protégé of the famous Jean-Martin Charcot, Pierre Marie met two patients suffering from acromegaly at the Pitié-Salpêtrière, at the request of his mentor.
Cornelius Magrath, who was 2.26 meters tall. In the years that followed, many other scientists reached the same conclusions as Cunningham, such as the American neurologist Charles Dana, the English physician Woods Hutchinson and the Frenchmen Edouard Brissaud and Henry Meige. As the discoveries were made, it became clear that both disorders had the same pathogenesis but that the disease was different depending on the age at which it occurred.

**Treatment approaches**

As scientists began to understand the disease better and better, the time for treatment finally arrived, at the turn of the 19th and 20th centuries. At that time, the first attempts at pituitary surgery took place. In 1892, Ercole Sacchi and Guilio Vassale, two Italian surgeons, succeeded in removing the pituitary gland in cats. Unfortunately, two years later, they declared that “the pituitary gland... is vital to the body. Its function consists in the elaboration and endocrine secretion of a special product, necessary for the organism”. Even if their attempt finally turned out to be a failure, the experiences of our two Italian surgeons allowed us to understand the role of the pituitary gland/hypophysis in metabolic functions and growth. At the same time, the first surgeries on people with acromegaly were performed. In 1893, British neurosurgeons Richard Caton and Frank Thomas Paul operated on a patient with acromegaly who was suffering from terrible headaches. Unfortunately, they were unable to reach the tumor. However, they did manage to relieve the sub temporal pressure, allowing the patient to have a better quality of life and greatly reduce the headaches. It was a semi-success that paved the way for about twenty years to this type of operation. Back then, it was not possible to cure the patients, but from the beginning of the 20th century, it was possible to give them a little more comfort.

In 1906, a major advance was made. It came from the Austrian surgeon Hermann Schloffer, who successfully removed a tumor of the pituitary gland via the transsphenoidal route. The following year, his compatriot and colleague, Julius von Hochenegg, carried out the first trans-sphenoidal approach to acromegaly. A major breakthrough, which made the headlines in international newspapers. In its edition of 10 May 1908, The New York Times headlined, with a backdrop of rivalry between American and European scientists:

“Acromegaly cured; operation successfully carried out by Professor Hochenegg of Vienna.”

American surgeons, who by the reluctant consent of their European colleagues, are now ranked at the top of their profession, will be interested in the brilliant achievement reported last week at the Berlin Congress of Surgery by Professor Hochenegg of Vienna. Professor Hochenegg told how he successfully operated on a case of acromegaly, a disease that causes strange and enormous enlargements of the bones of the hands, feet and face. The patient on whom the operation was performed was a young girl. She showed the usual symptoms of brain tumors and a marked disturbance of her vision. The diagnosis having been confirmed by X-rays, Professor Hochenegg moved the girl’s nose to one side, cut the thin floor of the skull and then removed the tumor from the pituitary gland, which was shaped like a gland hanging like a cherry, from the base of the brain. The difficulty in reaching the acromegalic tumor was such that the surgeons were rather reluctant to operate on it. It is said that none of the operations reported before last week had been successful; but the girl from Vienna left the hospital six weeks after Professor Hochenegg’s operation, her health having completely recovered. Acromegaly is not uncommon in the United States, but as a result, the Germans say, it has baffled American surgical skills.

In the decades to come, two routes were favored for operating on people with acromegaly. The trans-sphenoidal route, and the trans-cranial route, which will gain in popularity from the 1920s onwards. The development of endoscopic techniques and microscopic surgery from the 1930s onwards enabled a new direction to be taken, particularly thanks to Canadian neurosurgeon Jules Hardy.

Despite this progress, pituitary surgery remained very complicated and often led to complications during and after the operation. Many patients died on the operating table and in the days that followed. Although the successes of pituitary surgery were spectacular at the time, they were rare, and this fact helped another treatment approach to develop itself: radiotherapy. The principles of radiotherapy were discovered at the end of the 19th century, and its practice spread widely and very quickly, from the beginning of the 20th century. In 1909, the French radiotherapist Antoine Béclère succeeded in shrinking a tumor of the pituitary gland in a young woman suffering from acromegaly by the repeated use of radiotherapy. Radiotherapy was used for the most part in the decades that followed. Numerous advances in radiotherapy enabled this period of time, including better dosage and better knowledge about the frequency of sessions.

In 1945, the Growth Hormone (GH) was finally isolated by the Chinese-born American scientist Cho Hao Li. It had been discovered 25 years earlier, in 1920, by Herbert McLean Evans and Joseph Long. Cho was also able to determine its molecular structure. This was a major discovery that led to many advances. Shortly afterwards, Geoffrey W. Harris, a British neuroendocrinologist, succeeded in demonstrating that pituitary secretion is controlled by the hypothalamus. This process took place through release factors transported from the hypothalamus to the pituitary gland via the pituitary stem. As the role of the hypothalamus came to light, progress was made, and research during the 1950s, 60s and 70s accelerated. In 1977, the Nobel Prize for Medicine was awarded, in part, to Andrew V. Schally and Roger Guillemin for the identification of several hypothalamic factors including growth hormone-releasing hormone and somatostatin. Today, somatostatin plays an important role in the treatment of patients with acromegaly. Analogues of this protein hormone, which inhibits the secretion of growth hormone, are now commonly used, such as octreotide and lanreotide. These drugs used to be given several times a day by injection but advances in technology and research have now made it possible to use a single injection per month. According to Orphanet, these analogues “normalize growth hormone levels in about two thirds of those treated; after 6 months of treatment, they also lead to a reduction in the volume of the adenoma.”

In the end, the history of acromegaly is quite similar to the patients’ journey. Just like the patients, it took an enormous amount of time to identify the disease. This identification, which can be attributed to Pierre Marie, was also made possible thanks to the work of many other scientists such as Johannes Wier, Nicolas Saucercotte or Vincenzo Brigidi. It was often confused with other diseases and the
slow progression of the disease did not help to understand it more quickly. Today, the two preferred types of treatment are surgery, which has obviously improved considerably since the end of the 19th century, and drug treatments. Radiotherapy, on the other hand, is now only used very occasionally. It is also important to remember that the objective of acromegaly treatment is twofold: it is necessary to stop the progression of the tumor and thus reduce the symptoms, and to normalize the rate of growth hormone in order to halt the evolution of the disease.

According to the French Rare Diseases Portal, today:

“Acromegaly research focuses on four key areas:

1. The search for increasingly effective and better tolerated drugs.
2. Assessment of the long-term evolution of treated and cured acromegaly compared to acromegaly with only partially reduced growth hormone levels.
3. The study of the role of excess growth hormone in the development of tumors, especially in the colon, and in the development and evolution of heart problems and high blood pressure.
4. Research into the causes and mechanisms of the disease.”

As Marie Hélène Boucand points out in Une approche éthique des maladies rares génétiques (An Ethical Approach to Genetic Rare Diseases):

“The patient affected by a rare disease experiences the distressing singularity of being ill without corresponding to the usual representations of other patients.”

Sources:
10. Marie P (1886) On two cases of acromegaly: marked hypertrophy of the upper and lower limbs and head, Rev. Médecine 6, 297.
11. Charcot JM, and Marie P (1886) On a particular form of progressive muscular atrophy, often familial, starting with the feet and legs and later reaching the hands, Rev. Médecine 6, 97