Arnold Munnich

Personal Details

Name	Arnold Munnich
Dates	Born 1949
Place of Birth	Paris
Main work places	Paris
Principal field of work	Medical genetics

Short biography

After training in medicine and paediatrics in Paris, and a PhD in biochemistry and cell biology with Axel Kahn, Arnold Munnich succeded Jean Frezal as head of Medical Genetics at Hopital Necker, Paris. His research has focused on the molecular basis of paediatric genetic disorders, especially in relation to possible therapies. He also acted for 5 years as scientific advisor to French President Nicolas Sarkozy.

Interview

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INTERVIEW WITH ARNOLD MUNNICH, 9th JUNE 2013

PH = Interviewer (Peter Harper)

AM = Arnold Munnich

PH It's Sunday, June 9th and I'm speaking with Professor Arnold Munnich at Hôpital Necker in Paris. Arnold, can I start at the beginning and ask when were you born and where?

AM I was born in Paris in October 1949 and I have been brought up in Paris and spent most of my life in this country and in this city.

PH Did you come, may I ask, from a medical or scientific family?

AM My father was an extremely skilful and talented engineer. He was the son of immigrants. My grandparents emigrated from Sweden to France in 1910 and I shall come back to this in a minute; my father was the third of a family of three, and he was the brightest. He had excellent scores at school and he passed the most difficult concours examinations and went into the highest scientific school in France called l'École Polytechnique. It's a school that was founded by Napoleon to train and educate the best pupils of the nation and he aimed to become an engineer, he became an engineer, but it was just before the war and because he was Jewish he was expelled from the army in 1939. And then because of the situation he enrolled in the Scouts; he was already a boy scout before the war with my uncle, whose name I've received because he was killed by the Nazis. And my father enrolled in the Scouts, the Boy Scouts, and at some point they have to live in South France after the débâcle, you know the disaster, with many young Jewish Scouts. Some of them stayed there, some of them flee to Switzerland, many were kept. And my father was ordered to go to Algeria to take care of the Jews in Algeria.

And so my father went to Algeria in 1941, I think, through Spain. He had to cross the border and go from Spain to Algiers. And he was sent to a city called Constantine, eastern Algeria. And when he arrived to Constantine, a very nice Jewish community, he was sent to his Algerian counterpart and he met a young lady, charming, whom he married and she's my mother. So they spent the end of the war in Algeria and they came back to France in 1944. When the Americans and the Brits disembarked in Algeria in 1942, my father not only being a Scout decided to go back to the army and he was enrolled as a mechanic for the Spitfire. He was fixing the planes for the Brits and the US and he was on the ground in a city called Blida in southern Algiers. He was supposed to repair the planes and to fix them so that they can return to fight.

And in a sense Algeria has saved my father and saved my family. They came back from Algeria in 1944 and my father, who was a soldier and a lover of France decided to return to the army. So he took back his position, the one that he has been chased off. But again he was the third of a talented family and the first of the three was Arnold Munnich and he was also a fighter and he was killed during the first days of the war in northern France. And this name is very surprising: Arnold is not a very common name especially for a Jewish family from Poland and Sweden. And I have only recently understood the sense, the origin of my name. Maybe it's interesting; I don't know? It's always interesting to look at the names. The Jews used to give to a new-born, to the first new-born of a generation, the name of the paternal grandfather. And my Uncle Arnold was killed so my parents decided to give me his name. So the question is: why was he called Arnold? Because I took over his name but why is he called Arnold? It's interesting because there are not many Jews with this first name.

When they were in Poland they used to have two first names: the two were very biblical names and they used to translate one of the two into a more lay name, you understand? And my uncle's name

was Shmuel Aaron, Samuel Aaron. And he was given Samuel as a Jewish name but Aaron was turned into Arnold and this is because it was the name of his grandfather, my grandfather's father from Poland in 1865. So this was a very strange name. My family name was strange, not a good name for a Jewish family to be called Munnich; very painful. And in fact it was Minik in Poland and it's probably the acronym of a sentence, a verse of the Song of the Songs ("Chir hachirim" in Hebrew). Possibly the first letters of a given verse of the canticle and there are several families like that: MUNK, MINIK, MINK all this. So my name was Aaron and transformed to Arnold, Minik transferred into Munnich. But the strange thing and very interesting thing is that my father was very, very chauvinistic, was a lover of France and after coming back to Paris he decided to re-engage into the army and spend his whole life in the French army.

And his family originated from Sweden but they escaped from Poland again. The interesting discussion that has been always extremely puzzling for my brothers and myself is why did my grandfather, my father's father, decide to move from Sweden to France. Why? Why? The Jews were very happy in Sweden. They were very fortunate: they were well treated, protected, and they found work, respect, the liberty of their belief and practices. But I have understood, along the years, that they were a large family of 10 boys and girls and there was a lot of competition between the first born, Herman, and my grandfather was younger. And my great uncle was extremely successful and very Germanophilic; very, very German. The Jews there were fascinated by Germany. It's very difficult to understand this today; how chauvinistic the German Jews, the Swedish Jews were. Nowadays, it is hardly understandable. My great uncle was extremely Germanophilic and extremely successful, and my grandfather was probably a little jealous and upset about that, probably fought with his brother and at one stage he became extremely Francophilic because his brother was Germanophilic. And after, you remember the history of the Dreyfus affair?

PH I do.

AM It's extremely important here because it impacts the story of my family and many other families. And many Jews from Poland, Sweden, Germany etc. decided that the country that can fight for a little Jewish captain and give him the credit of the truth is a country where the Jews can stay and live, you understand? So my grandfather decided to quit Sweden where he was happy, to quit his family in a very competitive ambience, I think, and he decided to move to Paris in 1910. And his wife joined him shortly after and they brought up a French family and my father was extremely attached not only to Judaism and Sweden but also to France. And he has brought up us in very loyal, faithful, honest and committed manner, you know? So he was an engineer, I am a doctor, my two brothers were very successful too, but the three of us we share this commitment to France despite all these extremely painful episodes.

PH So did you go to university here in Paris?

AM Yes. After having passed my Baccalauréat degree I went to medical school immediately because in a sense the weight of my father was so heavy that I felt I could not compete with him in the field of mathematics and physics. I had to find my own way. In his view I was supposed to follow him but I always felt unable to match his talent and skills. So I decided to take another direction and I registered to medical school just after my Bac. And I studied very quickly, and I finished on time and passed the internship. It was extremely competitive because all of us were competing but a small number of applicants would win. It was enormous; the ratio was probably one tenth (1:10)

PH And this… was this here at Necker or more generally?

AM More generally; the Paris School of Medicine. Because at that time the medical schools were not split; there was only one medical school and they were split just after May 68, this May Revolution where all the academic system had been changed. And then the Medical School of Necker was created and I was transferred from the Faculté de Médicine de Paris into the Faculty of Medicine Necker. You had

to choose between several and I was allotted this one. So I spent my medical school here and passed the internship and I have started as a paediatrician. In fact I was fascinated by paediatrics and I started as a paediatrician.

PH So at what point did you come into contact with those workers in metabolism and genetics that were so important for you later?

AM At the end of my medical school, medical studies, I have met with a very, very charismatic person. His name was Jean-Marie Saudubray.

PH I knew him.

AM You might have interviewed him by the way; he's interesting.

PH He's still living?

AM Yes. And by that time Jean Frézal was competing for deputisation so he had left the department to Saudubray. Frézal was committed with Jacques Chirac and Saudubray was his assistant but in fact he was the acting chairman of the department and this guy was extremely charismatic. He was not only an excellent paediatrician and very good specialist of metabolic disease but was also extremely charismatic and he was able to generate vocations, you know. So I was fascinated by this combination of clinical and scientific issues in the metabolic diseases. Sometimes Jean Frézal was there but Jean-Marie was extremely good at teaching us clinical features, the clinical symptoms, the clinical story of disease, clinical management, dietary management, etc. But when Frézal was there, it was different because he had a much higher viewpoint because he was trained as a geneticist and he had not only the clinical expertise but also the scientific expertise. He had, to my sense, less clinical skills but a higher scientific view. He was less committed into the clinical. He had less empathy and sympathy for the patient and the children but he had a viewpoint that was, to my sense, higher.

So the combination of the two was extremely exciting. When I became an intern, I say to myself that I had to follow the pathway of Frézal and to go to the university of science. So after having got my degree as an intern I registered as a student in the university of science and started my bachelor and masters in biochemistry to have a more solid background in biochemistry. And at one point we had to go for a stage in the laboratory till the end of the master. I was already an intern by that time taking care of the children and had not much time to look for a good stage, good laboratories, and I was suggested to contact a man who has been extremely important for me, very important. His name was Jacques Hanoune. Jacques Hanoune (etymologically, the "charming") was an endocrinologist at Mondor Hospital. He was born in Algeria and so I felt very comfortable with him and I met with him following the suggestion of Milgrom and Robel, two teachers of my master course. He was as warm as my mother was. He reminded me of my family; my mother's family was very good to me.

You have to know something, Peter: at that time, this is not easy to say, but this country was still anti-Semitic. Don't forget that; we are not long after the war. And being a young Jewish fellow would reduce enormously my chance to get a position; enormously. If you write this in the book I should be sued for that or blamed for that but this is the truth. At least, it is what I felt. And along those lines, one day, Frézal noticed my commitment to genetics and called me in his office. I was sitting in front of him as you are here and we discuss and he say to me, "Arnold, vous êtes Juif?" I, c'est incroyable, heh? I didn't understand and he wanted me to confess that I was Jewish. I say, "Yes, sir, I'm Jewish''. This is why I was more secure under the protection of Hanoune because he was Jewish and also to Dreyfus, because they were Jews. They were very left-handed but I felt I could not be threatened by them because I was a Jew as they were. You see what I mean? Because the rest of this generation like Grouchy, Lejeune, all these guys, they were thought to be anti-Semitic.

And I was ambitious because my father did so well. I had to prove to him that I was able to have a career, to have a personal and professional success. I was deemed to succeed because we were

survivors and, as a generation we had to succeed and prove that we were able to match the courage of the previous generations. So it was for many of us: we felt that we had to succeed, it was mandatory to succeed. You see what I mean? So it was very important to get tenure and positions were extremely scarce at that time; very few, very few. And Frézal was playing with me like cat and mouse, you know? It was very painful and I was calculating, because there were competitors of course and until the very last end I was wondering whether he would keep me or throw me; this is the truth. And this is why I could not leave France for long, because most of my good friends went to America, to UK for long post-doc etc. but I felt frankly that if I have gone for too long and stop writing papers for him or preparing the slides for him or preparing you know the duties for him, he would have forgotten me, Nepotism was an issue, I must confess that. You have this sense? You have heard that before?

PH I have many times in interviewing people, yes.

So Arnold, did you do a thesis on this phase of your early research?

AM Yes, I have had excellent mentors. Hanoune was very good to me I was a decent paediatrician but I knew very little in science and the first time I met him in 1976 in his laboratory at Mondor Créteil we felt we went very well along together the two of us. And he spoke out to me very nicely and he say to me, "Arnold, you have to speak fluent English; you have to be extremely comfortable in English; you have to fight in English, to answer in English, to challenge your competitors in English. Your competitors are not in the hexagon, not in France; your competitors are abroad in the UK and Germany, in America, in Canada." So I shall always remember, "Don't tell me any longer that "dix moins six molaire"; you have to say "ten to the minus six molar"; "ten to the minus 12 molar". "You have to be fluent in English; you have to write English, to speak English, to answer, to fight in English. And if you stay in your language, you are done; you are lost." And he converted me in that sense and it was an echo to what my father said. My father said to my mother when they married, "I want my sons to be good Jews; fluent in English and fair guys." So this was the roadmap of my father to be a good Jewish guy, to speak English and to work hard.

PH So the subject then of your thesis?

AM I started with the characterisation of beta adrenergic receptors; it was extremely interesting because it was like enzymology: I had to learn enzymology and Km, the KI, the Vmax etc; this was not taught at that medical school. The level of teaching at medical school was a disaster; it was almost zero. The teachers were bad and what they taught was not interesting at all. At university of science and during that stage, I really learned a lot, it was not only a training in science but also a "rehabilitation" by the science, you see what I mean? I had to be reformatted by the science. We learnt enzymology and biochemistry of the membrane receptors. So I did my first thesis on the characteristics of beta adrenergic receptors in the liver and after that I resumed my internship and after having completed my internship I applied to Axel Kahn to do a PhD thesis and this was the time when the genes for glycolytic enzymes were cloned, and some of them were cloned by Axel like the pyruvate kinase cDNA, the aldolase B cDNA by Fanny Shapira and Jean-Claude Dreyfus and many of the glycolytic enzyme genes.

And I said to Axel that I would be interested in studying the regulation of those genes' expression and I felt interested in studying the impact of diet and hormones on the level of glycolytic and neo-glycogenic enzyme gene expression. So during 2 or 3 years I did experiments on rats, either fed or starved under various endocrine conditions and I wrote several papers and I was very proud to be the first one to show that cyclic AMP not only enhanced a gene expression but cyclic AMP could also block completely a gene expression. So we ended up with a compound that was able to regulate glucose metabolism in a very concerted manner, stimulated glycogenesis, inhibited glycolysis. It was very consistent. We wrote good papers in good journals and I got a PhD thesis in 1990. Then I came

back to the clinic with Frézal. And at that time I was not yet sure that he would keep me; he was still playing with me like mouse and cat. And Saudubray also was rather wary with me. They have not hurt me but in a sense it was a painful life and I was fighting, fighting. And I say to myself, "If by chance I succeed one day I shall bring up as many pupils as possible from all over areas in the world, whatever their belief, their origin, the colour of their skin." I decided to do exactly the contrary of what this guy did to me. It was sometimes very bitter. You understand this bitterness?

PH I do.

And this is as recently as 1990?

AM Yes, 1995.

PH So at what point did you obtain a secure post?

AM It was very, very late. I was extremely insecure until 1990. In 1990 Jérôme Lejeune stepped down and Jérôme Lejeune hated me for all those reasons; he hated me, Peter. Not only because I was Jewish but also I was a fellow with Frézal and those guys were fighting each other all the time: Grouchy, Frézal, Turpin, Lejeune. So Frézal was so talented, so smart, so elegant, so knowledgeable and Saudubray was good at the clinic. Frézal had the novel ideas, he was, you know, introducing molecular genetics in paediatrics. He was introducing science into medicine and it was fascinating for me. And when I got my PhD thesis, or shortly before, Frézal told me that he had decided to try to give me the tenure position of Jérôme Lejeune. And Jérôme Lejeune was extremely unhappy about that; he didn't want me to take over after him and then the dean decided to give me his tenure position. Michel Vekemans, a very good guy from McGill, was recruited to do cytogenetics and I was recruited to take over on the position of Lejeune but to go along after Frézal. So I took over after Frézal and at that point Saudubray put me out. He said to me. "You will not inherit the metabolic disease; you will not inherit that. Go and do genetics. You will not become my successor."

I was a lover of metabolic disease but at that point, because I was supported by Frézal, I understood that metabolic disease would not be my job in the long term future. Yet, I started to do lab work with Jean Rey on phenylketonuria but also some metabolic disease that Saudubray was not interested in. And I started the lab from zero, Peter; zero, absolutely nothing, nothing. Not a bench, nothing. So with Stan Lyonnet we wrote the first paper in English, he went to the Pasteur Institute to run the sequences of the PKU gene of the patients. We wrote a paper, we had a very small bench, that big [indicates], for the 2 of us, Stan and I. And we had no financial support, no technical support, no money, no funding, nothing. And day after day I have built this laboratory from zero.

PH So this was the first molecular genetics lab in Necker?

AM Yes, absolutely.

PH Am I right that Frézal's gene mapping studies had really been exclusively with protein markers or had he begun to think in terms of molecular markers at all?

AM Very late. It was mostly protein. By that time what was very striking for me is that his research was completely split, separated from his clinical activities. His clinical duty was a clinical genetic unit with genetic counselling and some metabolic disease but his research had nothing to do with the patients and he was working on the genetic map of various species with Marie-Claude Hors-Cayla and Nguyen van Cong. There was absolutely no link between clinical and scientific questions; nothing. Two completely different worlds. And it was obvious to me that one had to merge the two concerns; clinical issues, scientific issues. But he was not interested in that; he was only interested in mapping some human genes as Grouchy and Dutrillaux did on the chimpanzee. The FISH studies were done by Marie-Geneviève and Jean-François Mattei but what he did on his side was mostly the hybrids.

PH I remember that work.

AM He was very good theoretically but he was not a talented, skilful technician. He knew nothing about science technically. He was referring all that to people that were working for him but he did not commit himself into practical life of a laboratory like I do myself. He would give incentive, directions, instructions but he would never commit himself into doing the work, you know; he was delegating work. And I did not like that, you see. What I wanted was to put my hands into that. So I did many efforts to bring together the clinical and the lab and to focus on the issues of human genetic disease. But he was not happy about that and Saudubray was not happy about that either.

PH So at what point did Frézal retire and you take over direction?

AM 1992. I got the position of Lejeune in 1990 but Lejeune stayed there; he didn't want to see me. So he was in his office here, in front of you here, and I was in the old building, called Lamy building where Frézal had his laboratory. I was tolerated in the clinical unit but Saudubray was with me. So I spent 2 years into the old laboratory and in the clinic while Frézal was still there. And the interesting thing is that in1988, just before I got my tenure, the first French Téléthon was launched. It was a big success and they raised a huge amount of money and then Frézal applied for a call that AFM have launched to map the gene for spinal muscular atrophy. It was in 1988. And at that time Frézal got the money from AFM, from Barataud, to build a laboratory dedicated to the mapping of disease genes in humans. And at that point Frézal, who did not know how to handle a laboratory, passed me the responsibility to build the laboratory. Then we moved from this old building to this building here and this building has been funded thanks to Frézal by the French téléthon. What for? To map the disease genes in humans starting from spinal muscular atrophy (SMA). And this is what we did, with Judith Melki and Jean Frézal. So I got tenure in 90, I took over after Frézal in 1992 and we started here in the laboratory in 1988. We mapped the SMA gene in 1990 and identified the gene in 1995.

PH That, am I right, was with Judith Melki?

AM Yes, yes.

PH So she was part of your team then?

AM Yes, she's fantastic.

PH Were you still trying to work with the genes for inherited metabolic disease at this time or how did that side progress after you'd been blocked from the more clinical aspects by Saudubray?

AM Frankly speaking we were not in a situation to engage a lot of work for mapping of disease genes. We started with SMA, but remember it was very difficult; hundreds of RFLPs, thousands of blood samples, enzymes, digestion, it was an enormous work with very little money. So the only serious gene mapping that we have done was the SMA gene. For the rest it was mostly molecular characterisation of mutations in known genes; in genes that had been cloned by others. At the beginning I tried to fill the gap with Saudubray and tried to work on the OTC gene, the gene for ornithine transcarbamylase, because we had so many patients and I was mostly concerned about the patients. And we started the first prenatal diagnosis for this and other conditions. So we keep along this way with OTC gene, for PKU gene and the SMA gene identification. But apart from that we had no resources, no force, and very little support. Have you heard about a guy called Jean Rey?

PH Yes. I heard about him from Jean-Claude Kaplan.

AM Jean Rey was in fact the most talented disciple of Frézal. Frézal liked him enormously and Jean Rey and his wife, Françoise Rey, were in charge in phenylketonuria. And by that time Jean was the Dean and I had so little support that with Stan we decided to work on PKU to get the credit of helping Jean Rey who was the Dean. This was very opportunistic from my side but I knew that I could not rely on Saudubray, and very little on Frézal at that time. Now he has changed his mind. But by that time my only support was Frézal, partly, and Jean Rey. And this is why we have started to work on the SMA

gene for Frézal and on the PKU gene for Jean Rey. At that time you had to have a mentor. Nepotism was the rule, it was not the exception.

PH Un patron.

AM A patron. You had to work like a slave for a patron otherwise we were killed. This is how it was, believe me. Is it a surprise to you?

PH It is a surprise to me that this continued in such recent years. I knew that it was the rule maybe 30, 40 years ago but to see it continue to such a recent time, that does surprise me, yes.

And out of all of the work you've done over the past more than 20 years, we don't have time to go over everything but is there one area that gives you particular satisfaction that you've been able to work in? Because you've had so many publications but perhaps there is one field that stands out?

AM There are many [pause]. Lejeune used to say something very interesting: he said in French, "Je suis médecin par vocation et chercheur par nécessité". You understand?

PH I understand.

AM So I regard myself as a researcher by necessity but the vocation is to cure the patients; to reduce the suffering, for many reasons, personal and family. So to reduce the burden on the given individual. So finding a gene, understanding a disease mechanism is very nice, but if you're fortunate enough to bring it back to an improvement of the condition of the children, this is a grace. You see what I mean?

PH I do.

AM So what I'm proud of is to bring the journey from gene identification to the first clinical trials. And when we've done this loop then I'm extremely happy. And there are a couple of examples: the first is achondroplasia. Have you attended the session yesterday?

PH No, only the opening part.

AM Not the 5 selected abstracts?

PH No, I could not.

AM The first clinical trial on achondroplasia, we found the gene in 1994 (FGFR3) and we have understood part of the disease mechanism with Laurence Legeai-Mallet and addressed the first clinical trials and now we are in Phase 2 of a compound that is inhibiting the activating pathway in achondroplasia patients. This I'm very proud of: to bring a story from the gene identification to the clinical trial. Same is true for Friedreich's ataxia also. I'm very interested in that because we have been fortunate to understand what the disease mechanism was; it's in a Nature Genetics paper by Agnès Rotig and Pierre Rustin in 1996. And we have launched 2 of the 3 clinical trials for Friedreich's ataxia. Not completely successful but it works for heart, for instance, and some neurological improvement. This I'm very proud of. So the beauty of our work I think is not only to give personal excitement about science but to be concerned by the transfer of this science to clinical application. This is what medical genetics is for me; it is not only the satisfaction of our curiosity; we are deemed to transfer this knowledge into benefit for the genome. And this is my main challenge; to put as much cases to the step, to the point of clinical trials. The beauty is there. Can I take one other example?

PH Of course.

AM Because you know Valérie Comier?

PH Yes.

AM The bone dysplasia person who took over after Maroteaux. She has mapped a gene for Ghosal syndrome. Ghosal syndrome is an extremely rare osteopetrosis; three families worldwide. But she decided to map and identify the disease gene and she ended up with identification of thromboxan

synthase which is a gene that is involved in platelet aggregation and also in bone remodelling. And when she found this gene we published a Nature Genetics paper and I said to her, "We are going to patent this gene." And she said to me, "You are crazy? Why would we patent a gene for 3 families worldwide?" And I say to her, "Look you have put your hand on an enzyme that when inhibited makes the bone much stronger; suppose that you medically, pharmacologically inhibit this enzyme, you will reinforce the strength of the bone and then you can launch a new category of compound for osteogenesis imperfecta and osteoporosis. So you start with 3 families with osteopetrosis and you end up with 800 million people with osteoporosis." So we have started to transfer this into a clinical trial about inhibiting this enzyme in osteogenesis imperfecta and osteoporosis.

So what I am very proud of is, first of all, my collaborators. I have had a beautiful life thanks to them: Valérie, Stan, Judith, many others. All the contrary of my mentors, and to have had the grace to bring some questions from gene identification to the first clinical trials. This is my, this is a privilege.

PH **It's wonderful to have had that opportunity and it strikes me that this is now becoming, perhaps now the main role of medical genetics in a wide range. I mean we ourselves have encountered it for myotonic dystrophy, Huntington's, tuberous sclerosis with my Cardiff colleagues.**

AM Lovely. I like this guy, he's charming.

PH **This is Julian Sampson, my successor.**

AM I know; we have spoken highly of you. I like this. He has helped me for my patients. It's brilliant and it works. You must be proud of him.

PH **I'm very proud.**

AM He's charming; I like him enormously. We are in close contact.

PH **Good, good. Now I want to ask you one thing quite on a different line: this is your experience of being an advisor to politicians because I think I'm right that you've been advisor to President Sarkozy?**

AM Five years.

PH **How did this come about and what did you learn from this?**

AM I'll give you a short Nature paper, News and Views, that I have written exactly on that, if you are interested.

PH **I should like it, but I'd like to have it in your own words also.**

AM It's a love story in a sense, for Nicolas, he's such a charming person. One day I wrote an article in Le Monde and I was upset about the excitement about the genome, sequencing the genome because on the TV all the companies were claiming that all the problems would be solved, and all this excitement about the genome was extremely bothering to me. So I wrote a pamphlet like, you know, a little provocative; I like that. And I sent it to Le Monde and they published it. And one day I received a phone call from the mayor office in Neuilly "The Mayor wants to meet with you. He has read your article and is interested by the pamphlet. Could you come and have a breakfast with him?" It was Nicolas.

PH **[laughs]**

AM That was 1990. I was not particularly right-handed or left-handed, you know, I was very pragmatic. And I met with that guy, believe me, and we fell in love with each other like two, we were alike, he was so active, I am very active; he was an immigrant, I am an immigrant; he was a Jewish guy from Hungary, I'm a Jewish guy from Poland. And we felt so, like we recognised each other in some sense. And he was interested, I was interested by him and we have kept on writing and exchanging through

the years and he asked my help during the campaign because he has been challenged on difficult issues and he asked me to help him answering this question on the TV, on the radio, even in the meetings. And I say to him, "Nicolas, I do whatever you want but promise me that you don't recruit me. I want to stay in the laboratory." I say, "Promise." Fifteen days after having been elected he called me and "Do you want to become my advisor?" And I say to him, "Nicolas, how can I say no? But how can I say yes?" So he decided to let me be part-time and I started part-time with him and it has been extremely exciting because during this 5 years I have been able to inject new ideas for France. Because you have to remember that in France universities are not free as in your country; we are still living under the burden of a tradition in France which has a lot to do with what we have discussed before. Christianity, the Revolution, and royalty. And this is a burden on this country. Christianity and the Revolution, socialism also. And for all those reasons this is a very Jacobinic kind of organisation.

PH Hierarchical!

AM Hierarchical. And because the universities were so weak in France before the war and after the war those agencies have been created like INSERM and CNRS, to enforce French science. It has worked but at the expense of the universities that were weak and become weaker and weaker. And at some point Sarkozy's advisors suggested him to release universities, to get them their freedom to act by giving them autonomy. And the big achievement has been this one, to get the point where a university becomes free like you have Oxford and Cambridge and Bristol etc. And this was a revolution in France. And also to admit that not all medical schools are alike; some are better than others, which is impossible to hear in France because in this country everyone has to be even, equal. It's not equality, it's egalitarianism, you know; it's different. So this country has lived and still lives under the dogma of egalitarianism and cannot give credit to merit, to dedication, to effort, and this is what Sarkozy has imposed in this community, to change the paradigm, to accept that some are better than others; some are more committed than others, some deserve more money, more support than others simply because they are better.

And this was a revolution. And we have launched a call for the 5 best medical schools and we have massively supported 5 medical schools including this one. So I have been blamed for having favoured this one, which is not the case, and Strasbourg has one, Marseille has one, and Bordeaux has one, and Salpêtrière also. So they have invested, endowed 5 medical schools with a huge amount of money to hand them. So probably the main achievement is to have pushed autonomy of universities, including medical schools, and to have supported the best medical schools for education and research. But now the left is trying to withdraw all this. Politics, of course.

PH So this was for 5 years and now you are back, more or less full time?

AM Yes. Very happy.

PH [laughs]

AM Very happy.

PH Do you think that apart from yourself the others who have been involved politically from medical genetics have helped to raise the profile of the field? I'm quite struck by the fact that there's Jean-François Mattei who was involved and there was quite a tradition of important people from the field, I mean including Jean Frézal…

AM Frézal, Mattei.

PH Do you think this has helped to make the field recognised politically as well as medically in terms of its funding and support?

AM I think that the three of us have marked the land in a way. Jean Frézal has written for Debré the law of the academic hospital in France. This is the work of Jean Frézal. He has written the law, his ordinance

(Ordinance Debré) in 1958 which decided the two-fold appointment of some university hospitals. So the professor would be two-fold appointed: university and the hospital. If not they would have gone to private practice and that would have even further weakened the level of French universities. It was very important to retain the best in the university by creating this two-fold appointment; in centre hospitalier universitaire. This is the main achievement of Jean Frézal. As far as Jean-François Mattei is concerned, in our field he has been extremely, extremely contributive because he has created the speciality of genetics which did not exist. In 1994, he has created a speciality while he was a deputy, before he became a minister I think, about the same time, and this specialty did not exist beforehand. We were paediatrician, or neurologist, or haematologist by academic training and we would do our research, our clinical work in clinical genetics. But he has created the specialty because we had to split from paediatrics for instance, or from neurology. And this has not been properly understood by many of them. And we were regarded like cheaters, you know, like, how do you say, traitres?

PH Traitors.

AM Traitors. And by the paediatricians, but also the neurologists, by the biochemists, and it has been extremely difficult to build this speciality but now it's built and this is thanks to Jean-François Mattei. He has also created genetic counsellors that did not exist in France, extremely important also. And as far as nationwide is concerned he has been extremely instrumental for adoption, the rule for adoption is also his achievement. And he has also invested a huge amount of money in the rebuilding in the French public hospitals. So in many respects, he has completely changed the landscape in medical genetics but also in the social. The rule for research on embryo is also his achievement. In France, and I fully agree with this view, we consider that research on human embryo should be forbidden by law with derogations. The general rule is that research on a human being is forbidden; then you can derogate. The baseline is to forbid and to derogate when necessary. What the socialists want is to release, to allow the research on the embryos with some…

PH Exceptions.

AM Restrictions.

PH Yes.

AM Restrictions. But on the ethical standpoint we believe, we, the liberal and the right, we believe that it's very important to defend our ideas that you cannot change the law to deal with problems even important like science. We should stick to a regimen of interdiction with possible derogation. And in fact we gave a number of derogations for scientific issues but what we fight for is the maintaining of this regimen of interdiction with derogation. And what the socialists want to do is to release the research with restriction. And this is also to the credit of Jean-François Mattei who wrote an ethical law and this has been extremely important. So the contribution of Jean-Francois is the creation of the genetics speciality, the creation of the genetic counsellor, the funding of the public hospitals to be rebuilt, the law for adoption and the law, called ethical law that gives a frame to ethical medical practice. And this is credit, his contribution is enormous. It's enormous. And my contribution is to have accepted that we are not all alike and some of us deserve more support than others.

PH Arnold, I've been asking everybody that I've interviewed one thing, two things actually but one you've already answered, which was the area that you feel most proud about. But I've been asking everyone which people do you feel have had the most influence on the development of your career in medicine and science? Do particular people stand out?

AM It has to be only one?

PH No, you can have two if you wish, or even more.

AM [pause] The first one is the one who gave me my vocation as a doctor, who was my uncle; my mother's brother who give me the vocation. The second one is Jacques Hanoune who made the point

of the requested level of medicine in terms of scientific basis; he's the one who challenged me as far as my scientific background was concerned. So Jacques has been extremely important, pushing me to reinforce my basis in science and in English. The third one is Jean Frézal, who gave me my tenure, who selected me. He could have thrown me out; could have chosen somebody else and then I would be like in private practice. And the last one is Axel Kahn who admitted me in his laboratory for my PhD thesis. Axel was not a very easy guy, he was not very friendly with me, but I am grateful to him because he gave the possibility to have a good PhD thesis and a good training. And based on my training in his laboratory and on his accepting of Stan with me by that time, we have been able to start again from scratch, from zero, a laboratory of medical genetics in this hospital. So I am grateful to the four of them: my uncle, Jacques Hanoune, Jean Frézal, and Axel Kahn.

PH There are a lot of other things we could go over but we've spent a fair amount of time. Are there particular aspects that you feel we should have talked about but we've left out, or do you think that we have covered at least some of the main areas?

AM What I think we should have discussed is the medical application of our knowledge in genetics. I'm concerned about our patients, the citizens. They are going to face a huge amount of information on the genome that they are unable to handle, and the doctors are unable to handle either. And we geneticists are also unable to handle them. To my sense the medical use of genetics is of enormous concern. Are we going to do good or bad for the patient? There is a serious risk that we are going to harm with all this mass of information that we are unable to understand. Yes, I am extremely concerned about that.

PH Do you think perhaps that this is one of the most important roles for the medical geneticist, to be some advocate or intermediary between the patient and this mass of information?

AM Yes, it is exactly that. You have seen these papers from many authors where, doing their own genome sequencing, they found that they were affected with such and such condition and if this had been done prenatally they would have been simply discarded. You know the story. Jim Lupski was looking for his CMT mutation and he happened to find that he was had a stop codon for the adrenoleukodystrophy gene. He said to us, "Suppose that you would do my exome sequencing you would have discontinued this pregnancy, not for CMT but of course for adrenoleukodystrophy." And doing exome yourself you know that we come across a number of mutations in many cases, so how should we protect our population against this mass of un-understandable information? And I think that the Dutch are pushing much too much toward systematic exome sequencing and prenatal exome sequencing. I think this is extremely dangerous and my concern is to protect my patients and families from this nightmare. You know this sentence from the Ecclesiast? You know the Ecclesiast?

PH I do.

AM The verse from the King Solomon?

PH Which verse are you thinking of especially?

AM I can't give you the verse exactly. 'Abondance de savoir; abondance de souffrance. Celui qui augmente son savoir, augmente aussi sa souffrance.'

PH It's true up to a point, but I suppose my feeling would be until very recently our problem has been lack of knowledge rather than too much. Now things seem to be different and we have the problem of too much or too unselected information and that's why I feel, like you, that a role of the medical geneticist, probably now the most important role, is to be the person who can evaluate what is important and necessary and possibly what is harmful on behalf of the patient and the family. I think that most clinicians find this very difficult to do, at least outside their own special field, and most scientists find it almost impossible to do. So I think this is one of the main justifications for medical genetics being and continuing to be important as a specialty.

AM It's a necessity. Otherwise who and how should we filter information that is relevant for the patients? You probably, as we do, receive letters from patients who have been given results from their medical doctor and they're unable to understand what is written. They are scared and frightened: it's a nightmare. So now there is a pressure for the consumption of tests. For money issues they want to do as much testing as possible but no one is able to understand what is on the chart. At some point we should filter the information of the exome that we want to read, like windows, to select what windows you are going to read, and what windows you are going to ignore. But frankly speaking, the major threat is to spoil the life of the population with this mass of information if it is not selected properly. I think that the Dutch are going too far and too quickly ahead claiming for systemic exome sequencing. What shall we do with this information? It's impossible to handle it. So many results, that are very difficult to understand and to share with the patients. This should be regarded in a sense as modern eugenism; again in the name of science, as in the past! The spectrum of eugenism is still there. Very scary. Have you by chance ever seen the first article of the first issue of Annals of Eugenics? 1925. Have you seen this paper?

PH I don't remember it unless it was by Fisher? I don't remember it.

AM It's by Galton.

PH By Galton.

AM I'm going to show it to you because we have inherited all the collection of Frézal who inherited it from Maurice Lamy, who was given it by Debré. I am going to show you, before we finish, the first article of the first issue of Annals of Eugenics 1925. Believe me, it's scary. It's scary. It's exactly what's going to happen again. Here it's not anti-Semitism but it's just alike. So I am both extremely excited and concerned, as you are probably also.

PH Arnold, thank you very much. We must finish now but I'm very grateful. It's been a pleasure.