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SAMUEL REFETOFF, MD

Interview conducted by  
Michael Chappelle  
June 4, 2011

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## INTRODUCTION

Samuel Refetoff, MD, the Frederick H. Rawson Professor in Medicine, Professor of Pediatrics, Committee on Genetics and Director of the Endocrinology Laboratory at the University of Chicago, is recognized worldwide as the investigator who discovered and defined the molecular basis of the syndrome of resistance to thyroid hormone (RTH), appropriately called the Refetoff syndrome. In addition to RTH, he has identified two other syndromes: resistance to thyrotropin (RTSH) and the inherited defect that affects the metabolism of thyroid hormones through mutations in SECISBP2 gene. Over the past fifteen years, Dr. Refetoff's laboratory has taken the following approach in the study of inherited thyroid diseases: identification of new phenotypes through clinical studies of patients with congenital thyroid abnormalities followed by gene screen; the newly discovered gene defect is then characterized *in vitro* and by its introduction into mice by homologous recombination.

## BIOGRAPHICAL SKETCH

Dr. Refetoff was born in Bulgaria but emigrated to Belgium as a teenager, where he obtained his high school diploma from a French-speaking high school in Antwerp. A second emigration led him to Montreal, where he received a baccalaureate degree in 1959 from the University of Montreal, in French again. He then completed medical school in English at McGill University in 1963. Subsequently, he was an intern at Hospital Notre Dame in Montreal and resident at The Hospital of the Good Samaritan in California in 1964-65. It was during this year that he initiated studies on a victim of a car accident who presented with the combination of stippled epiphyses, goiter, deafness, and an elevated protein-bound iodine. It was with this index family that Refetoff syndrome was first identified. Dr. Refetoff then moved to Boston for another year of residency at the Lahey Clinic and then the Peter Bent Brigham Hospital to complete an endocrine fellowship in 1966-1968. It was during this time, and partly through his interactions with Dr. Leslie DeGroot, that he developed the clinical description of RTH. In 1969, Dr. Refetoff moved to the University of Chicago, where his group went on to identify two more syndromes: resistance to thyrotropin (RTSH), and a syndrome linked to an inherited defect that affects the metabolism of thyroid hormones through alterations in iodothyronine deiodinases. Dr. Refetoff was also the first to describe the molecular basis for familial dysalbuminemic hyperthyroxinemia, and he was the first to identify mutations in the thyroxine-binding globulin gene and a mutation in the thyroid transcription factor 1 (TTF1) gene that produces predominantly neurological defects. Dr. Refetoff's group discovered mutations in the monocarboxylate transporter gene (MCT8) and was able to link them to the Allan-Herndon-Dudley Syndrome. Although, Dr. Refetoff has 400-plus published scientific journal articles and has received numerous awards, including the Sidney Ingbar Award and the John B. Stanbury Pathophysiology Medal from the American Thyroid Association and the Robert H. Williams Distinguished Leadership Award from the Endocrine Society, he considers his greatest honors to have been his fellows, who now include thirty-five full-time faculty members at universities and research institutes around the world.

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## I. FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Dr. Refetoff, please tell me where your parents were born and what kind of education they had.

Refetoff: Both my parents were born in Bulgaria. My father had a university education in business. My mother didn't finish high school; she left one year before graduation and became a seamstress. After I was born, my mother didn't need to work anymore until we left Bulgaria.

Chappelle: What did your father do?

Refetoff: My father was a banker; he worked for the Franco-Belgian bank until the bank was closed during the Second World War, as it was owned by an enemy country, Belgium.

Chappelle: What was life like for you and your family in Bulgaria during the war and immediate aftermath?

Refetoff: During the war we had some deprivation in terms of food, and we had some bombardments by the allies because Bulgaria was an ally to Germany. But things did not get difficult for my family until after the war--during Communism--when families of individuals that are well-to-do were accused of amassing money by exploiting the proletarians. So, in fact, this is when my family left--about four years after the end of the war.

Chappelle: Where did you go?

Refetoff: Because my father worked for the Belgians, he thought that going to Belgium--we all left as refugees--that he would find a job. But, in fact, it was very difficult for refugees to be employed, even if he did work for the Belgians. As a consequence, we had to manage with some money that my father had saved in European banks and, eventually, immigrated to Canada.

Chappelle: What kind of student were you and what were your favorite subjects?

Refetoff: As any child of refugees, who had to work hard to make a living, we had no choice but do well at school, otherwise the guilt was quite strong if we didn't. I think that that has been a motivation for me and many other children in my situation. So I did quite well at school, both in high school and later in college. I was not a top student in medical school. I think by that time the guilt element kind of got diluted. [laughs]

Chappelle: What about extracurricular activities, sports, and things like that?

Refetoff: In high school I played volleyball, but later on in college I got involved in fencing and became quite good at fencing. I almost made it to the Olympics representing Canada. And I was also the captain of the fencing team at the University of Montreal. One of the reasons I think I was admitted to McGill Medical School is because they hoped that I may join the fencing team because the University of Montreal was leading in Canada and McGill wanted to move in that direction. They were really disappointed when I decided that the medical school was quite difficult and continuing fencing was not the right thing to do. [laughs]

## **II. EARLY CAREER IN SCIENCE AND MEDICINE (1955-1969)**

Chappelle: When did you first commit to a career in science or and medicine?

Refetoff: Well, that came in steps. As a child I was interested in biology; I was particularly interested in insects. As a matter of fact, I have continued to collect insects even after medical school. I have quite a good collection of butterflies. This brought me to biology. I studied biochemistry because I got interested in chemistry and wanted to continue in that field--getting a PhD. I then became a graduate student with Charles Phillip LeBlond, but didn't like it for various reasons--I think the atmosphere in the lab at the time was a little bit difficult. So being at McGill, I applied to medical school. As a medical student, I got interested more in the practice of medicine. I became very fond of Albert Schweitzer and thought to have a career in tropical medicine. For various reasons this didn't pan out, and--through a pure accident of encountering a family with a difficult endocrine problem related to the thyroid, which was the subject of my work with LeBlond--I returned to the thyroid and back to research.

Chappelle: Why did you decide to do your internship at Notre Dame Hospital?

Refetoff: I came to McGill from a French-speaking University. I didn't speak English and had some difficulties at the beginning in my first year of medical school. I was also at that time quite active in trying to reduce the animosity between the French and English speaking individuals, and I thought that--with two other friends of mine, one Greek and one, a Polish Jew--that we should attempt and break that separation by going into a French-speaking hospital to do our internship--we are the first to have done that, which turned out not to be very easy because there was a lot of resistance from both sides. But once this was done by us, in subsequent years this continued: English-speaking students from McGill went to French-speaking hospitals and vice versa, and now that is pretty well the custom in Montreal.

Chappelle: Why did you begin your residency at The Hospital of the Good Samaritan in Los Angeles?

Refetoff: After I finished medical school, I was accepted--with my interest in tropical medicine--to study at the London School of Tropical Medicine for which I received a scholarship from the Canadian government. Only months before I was due to go to London, I received a letter saying that the Canadian Parliament debated, concluding that there was really no problem in Canada with tropical diseases, and, therefore, they didn't see the value of supporting studies in this area. So I found myself without a position--my plans basically had to be changed. I looked through the medical journals and found an ad in the *New England Journal of Medicine* that there was a vacancy at The Good Samaritan Hospital. I think a resident became sick, developed leukemia, and had to drop out from the program, and so I was accepted in the program and moved to L.A.

Chappelle: What kind of physician/scientist were you thinking about becoming for a career?

Refetoff: I was still disappointed that I could not pursue my interest in going into tropical medicine--but had to compromise. It is at that time that I got involved with the family with an unusual thyroid presentation, which brought me back to my earlier studies with LeBlond on the thyroid, and gradually I developed interest in doing research.

### **State of the art thyroidology in the late-1960s**

Chappelle: What was the state of the art in thyroidology at that time?

Refetoff: Well, at that time--we are talking early sixties--there was no specific method to measure thyroid hormone. Thyroid hormone was measured indirectly as a protein-bound iodine. Basically, the amount of iodine in protein in the serum was quantitated as possibly representing thyroid hormone, and indeed in most instances it did. But there were instances when the iodine was contained in some other compounds producing results that were false. It is only in the subsequent years--with the development of radioimmunoassay, but first by development of the protein-binding assay by Murphy and Pattee, both of them from Montreal--a more specific method for measuring thyroxine developed. It took few years--early seventies--when Kenneth Sterling first published a method to measure triiodothyronine.

### **Discovering resistance to thyroid hormone (RTH)**

Chappelle: Would you speak to the medical-scientific stature of Dr. Lorren DeWind?

Refetoff: Dr. DeWind, who incidentally graduated from the University of Chicago where I was to go, was a practicing endocrinologist. I should say that, in my opinion--it may be biased--he was a very devoted and excellent

endocrinologist. He had no scientific background--he had published several clinical papers--he was astute enough to recognize the unusual presentation in the family that I ended up studying, and he encouraged me to do so. I was a resident at the time, first-year resident. He helped me to obtain a small grant from The Hospital of the Good Samaritan, which provided enough money to run tests on members of the family. This is what started this study of the first family with resistance to thyroid hormone.

Chappelle: And did you see your career then as having made a major shift?

Refetoff: The shift developed later, I think, as I continued studying the family and found it challenging. Step by step an interest developed in continuing and in pursuing a career in research.

Chappelle: How did you come to be an assistant in medicine at Peter Bent Brigham and a fellow at Harvard?

Refetoff: Because my plans to go to London had to be cancelled--and I had obtained just a temporary position at The Hospital of the Good Samaritan--I immediately made applications for the subsequent years. Although, after one year, Good Samaritan Hospital wanted to keep me for a second year--by that time I had already secured the position in Boston--not immediately at the Brigham, but first at the Lahey Clinic. following which I joined the Brigham as a fellow in endocrinology under Herb Selenkow, who was the thyroidologist at the Brigham. He became my mentor mainly because I developed interest in the thyroid.

Chappelle: Now in an earlier interview that you did for the Endocrine Society with Dr. Adolph Friedman, you sketched out the emergence of your interest in genetics and endocrinology, and you also talked about John Stanbury and Leslie DeGroot--that's on the record already--but I would like you to talk a little bit about the thyroid clinic and the ethos that was going on there and maybe something about the scientific backgrounds of Dr. Stanbury and Dr. DeGroot.

Refetoff: I was never at the Massachusetts General Hospital where the thyroid clinic took place. I got to know Drs. Stanbury and DeGroot because Dr. DeWind and myself had a little bit of difficulty convincing people that we had unusual cases and some difficulty in publishing our results. So at the Lahey Clinic it was Dr. Elmer Bartels that suggested that I go to Mass General and talk to these gentlemen, actually to Dr. Stanbury, and this is where I met Dr. DeGroot who undertook to send me back to L.A. to do some additional studies, and eventually resulted in the first publication, with as authors myself, Dr. Dewind and Dr. DeGroot. Both Drs. Stanbury and DeGroot have a very high standing in the scientific community, particularly in the thyroid. Dr. Stanbury was the mentor of DeGroot, and I think if it were not for the decision--or the inability--to pursue a plan to open a medical school at MIT

(Massachusetts Institute of Technology), both DeGroot and Stanbury would have been there still, and probably myself. Stanbury moved to MIT together with DeGroot. I had hoped to join them in the new medical school at MIT. And when those plans collapsed, DeGroot left for Chicago and eventually recruited me there.

Chappelle: What did he offer you?

Refetoff: Well, he offered me to be assistant professor, which I didn't expect to become at the Brigham probably for several years.

### **III. University of Chicago (1969-present)**

Chappelle: What were your initial responsibilities at the University of Chicago?

Refetoff: Well, like any young faculty at that time, we shared our time between clinical work and the laboratory. Clinical work was about fifty percent of the time; we had to attend general medicine, probably, three months out of the time, and we had a separate endocrinology ward, which now is nonexistent in most hospitals that I know. The laboratory work was done in the remaining time. Now, the universities at the time did not pressure faculty for income. In other terms, there was no direct accountability as to how much revenue there was from patients. So, young faculty had reasonably protected time to do their research. Also, research didn't cost that much--we made our own reagents; we didn't have to buy them. So with very little money we could undertake work. It took time, but certainly could be done quite cheaply. So there was not big pressure to obtain grants for support--certainly to support our salary and so forth, which is now the problem for young people, where they not only have to secure monies for their reagents and expenses that they have in the lab, but also for the part of the salary they obtain to secure and protect the time to do their research.

#### **Identifying three separate syndromes**

Chappelle: Among your scientific contributions there's been the identification of three separate syndromes: resistance to TH (Refetoff syndrome), resistance to TSH, and the defect in thyroid hormone metabolism--is there a designated name for that last one?

Refetoff: Yes. It's "defect in selenoprotein synthesis" because this is probably exactly what it is, because the mutation involves a protein that is absolutely required for the synthesis of selenoproteins.

Chappelle: Regarding these three syndromes, in what way does your research on them typify the approach you've taken in your laboratory?

Refetoff: Well, going back, I would say the approach began with my gradual involvement with the thyroid. The first family that got me into research had a genetic defect, so that introduced me into genetics combined with thyroid. I think my exposure with John Stanbury and Leslie DeGroot--John, especially, who has by that time identified several errors of thyroid hormone synthesis--had something to do with my continuing interest. At a certain point I took a sabbatical in Brussels, it was in 1975 where I was really introduced--by Gilbert Vassart--to serious molecular genetics. Then my career took off, combining thyroid and genetics. As for the methodology, I would say it evolved with modern development in research--identification of a new syndrome or a new genetic defect, search for the gene responsible for the defect, then producing a mouse model that would replicate the defect, because there is limitation in how much one can do with humans--especially the provision of tissues, which are not accessible under normal circumstances--and then studying in more detail the disease in the mouse, which then allows us to go back to the human and try to apply various forms of treatment. For many years the treatment for thyroid diseases was simple, namely, giving thyroid hormone, because most of the conditions identified were caused by deficiency in thyroid hormone. So as we learned more, we are now facing defects with thyroid hormone, Although the defect is absence or deficiency in thyroid hormone in tissues--this cannot be corrected by giving thyroid hormone because the defect is in the entry of thyroid hormone into the cell. So, we now have to be a little bit more creative and to develop treatments that are slightly different, which will bypass the use of thyroid hormone by using compounds that mimic the effect of thyroid hormone but are not thyroid hormone. So that closes the circle from the identification of a condition in the human, passing it to an animal--which allows in-depth studies--back to the human to try to remediate it and to correct it or cure it.

### **Resistance to thyroid hormone**

Chappelle: Would you bring your thyroid hormone resistance work up to date from Boston, tracing it through your early days in Chicago, and then up to the present day?

Refetoff: So my work on thyroid hormone resistance began in Los Angeles in the latter part of 1964 with the identification of a family with three children that had high thyroid hormone levels but did not manifest the expected symptoms and signs that would result from too much hormone, suggesting some form of hormone resistance. The initial work went to proving that the hormone was an authentic hormone, which was not easy at the time where there was no direct test to measure the hormone--which I just mentioned before--and it involved a rather more sophisticated biochemistry work, including the use of snake venom to prove that the thyroid hormones are L-amino acids. So with that, there was a long term of clinical studies, during which these children were given various forms of thyroid hormone and even some of the analogs of thyroid hormone in

studies that took us through 1972. There were two long visits, one in Boston--when I was here--of three months of the family of the affected three children, and one that followed in Chicago that lasted almost six months--the children stayed in Chicago; we provided them schooling and all the rest--which wrapped up the study. And I think we had a case that was convincing that these children had a problem with the recognition of thyroid hormone, namely, the receptor. And then there's a hiatus until 1989--because the receptor was unknown. And so in 1986 two laboratories, one of Bjorn Vennstrom in Sweden and one here in the United States--Ronald Evans'--identified the two thyroid hormone receptors called alpha and beta, one was in humans and the other in chicken. So with the identification of the thyroid hormone receptor, there was a tool to find whether any of those individuals had a defect in the receptor. By that time there were at least fifteen families already recognized to have such a defect, so we were not the only ones that identified mutation in the thyroid hormone receptor gene.

The first recognition that there may be a defect in the thyroid hormone receptor came from work at the NIH by Stephen Usala, who was working then in the laboratory of Bruce Weintraub. They did what is called linkage analysis and showed that the affected individuals shared an allele--thyroid hormone receptor beta--in common, which was not present in the unaffected individuals of the same family. Now, it is not that we sat idle during that period of time; we were doing the same work, and I was in communication with Steve Usala, with whom I became a good friend. We got contrary results. And--to be nice--I suggested that he not publish his results because they may be in error. It turned out that the error was ours; we mixed the sample of the grandmother and grandfather--the grandmother was mislabeled as the grandfather --and so we lost the linkage which requires that the allele co-segregate together with the phenotype, with the abnormality. We eventually found that this was the case by getting new samples--that was also complicated because the grandmother in the meantime died, but we recovered some of her cells that I had frozen, some skin fibroblasts. However, in the next step--defining the mutation--we kind of made it a little bit ahead of Bruce Weintraub by about a year--or maybe less; they were published in a different calendar year but probably the difference was only eight months--and from then on, more and more mutations were identified.

So that opened the field into understanding how those mutations caused resistance to thyroid hormone and why it manifested in a dominant fashion where the individual could synthesize both normal and abnormal receptor. And then the concept of dominant negative effect--which means that the mutant receptor interferes with the function of the normal receptor--arose and, I think, opened the field into understanding *some* aspect of how nuclear receptors work. Now as work progressed, we could go back to the original family--in which the inheritance was recessive--to find that they didn't have dominant negative effect--because instead of having a mutant receptor, they had deletion

of the entire receptor. So when only one allele was deleted, the other was normal--it didn't give any condition--but when both were dropped off, there was. And, in fact, out of now more than three thousand cases, this original family remains the only one that has the deletion of the entire gene. However--and I'm talking more about it because it's the subject of my interest--as many groups got involved in work with thyroid hormone resistance, it became apparent that there is a *subgroup* of individuals, representing fifteen percent of people that have the clinical phenotype, that have no mutations in their receptors. And that has been proven again by co-segregation analysis, proving that it's not that the mutation was missed, but it is impossible that this could be caused by mutation in the receptor. So this is where we stand now. Several groups, including mine, are working hard to find out what is the cause for this form of thyroid hormone resistance. In our case, we have already identified twenty-seven families that have the clinical phenotype that is undistinguishable clinically from those with mutation in the receptor, but they don't have mutation in the receptor. There are various theories. Naturally, good candidates are proteins that are involved in the complex that involves the receptor mediating gene transcription, but there is no exact cause yet known.

Chappelle: How is this current work being supported?

Refetoff: Well, I've been--I would use the term lucky because there is some degree of luck--naturally, luck is not sufficient to be funded, but looking at other groups that have done good work and have lost funding, I should include luck in the fact that I've been continually funded by NIH--only a single grant. I'm in my fortieth year and heard a week ago that I got five more.

### **Resistance to thyrotropin (RTSH)**

Chappelle: What is resistance to the action of TSH?

Refetoff: Similar to thyroid hormone resistance, where the thyroid hormone level is as high but the effect is reduced. All those syndromes of resistance are usually partial, they are not total, so reduced sensitivity should be the proper term. But resistance has become the preferred one--these individuals need higher TSH to function normally. In other terms, they have resistance to the normal amounts of TSH. And, again, those were identified, the first case, do you want to hear about it?

Chappelle: When was resistance to thyrotropin first recognized as a clinical entity?

Refetoff: A young pediatrician by the name of Michael Gottschalk at the University of Loyola joined the faculty and inherited a number of patients from his predecessor, who retired. Among them was a girl who was born with high TSH--thyrotropin--and was put on thyroid hormone. There were two other sisters that had the same situation. What he was astute enough to recognize is

that the first born, who also had high TSH, was not treated with thyroid hormone for three years until the second sister was born, and yet she developed normally. So he rightfully concluded that the TSH was high, but there was no need for thyroid hormone because the girl developed normally. So he contacted me, I reviewed the cases, and we decided under the circumstances to stop thyroid hormone. And in fact all of them had normal thyroid hormone level, but high TSH, suggesting that they really could compensate by having high TSH. We looked at the possibility that TSH had an abnormality--but it didn't--so we moved onto the receptor for TSH and found the first mutation that reduced the affinity of the receptor for TSH. Now I should say that my colleague and friend Vassart--several years earlier--found mutations in the TSH receptor that actually activated it and caused the opposite condition, hyperthyroidism. But those were all somatic mutation in thyroid nodules. At the time we recognized the receptor with reduced function, he phoned me: he said that he thought he had a germ-line mutation that activated the thyroid hormone. And so we got together and said we will publish it together, and in fact, that's what happened: Peter Kopp, who was at the time in Switzerland, identified a child that was born with hyperthyroidism and had a gain of function mutation that he worked out with Vassart. His case and ours were both published in *New England Journal of Medicine*--the gain of function and the loss of function mutation--which is how things should be done.

### **Defect in selenoprotein synthesis**

- Chappelle: I'd like to ask you a little bit about the SBP2 gene. First, what are selenoproteins? ?
- Refetoff: Selenoproteins are proteins that contain an unusual amino acid, which is selenocysteine, in one position or several positions in the amino acid chain, and that qualifies them to be selenoproteins. There are about twenty-four and probably more known selenoproteins that have various functions. In some of them, the function is unknown; this is a separate interest in that field of selenoproteins.
- Chappelle: What is the function or the functions of the selenocysteine insertion sequence-binding protein 2 gene?
- Refetoff: To form a selenoprotein one has to insert a selenocysteine in a position in the coding sequence of the RNA. The code for insertion of selenocysteine is a stop codon, a UGA. So in some instances that stop is recorded so that the protein synthesis is not stopped but a selenocysteine is inserted, and then that allows for other amino acids to be added in the sequence until a true stop occurs. Now what determines that a stop will be recorded in order to put the selenocysteine into the protein chain is a signal that is contained in the non-coding sequence of the RNA. To recognize that signal, SBP2--binds to that signal and determines in the synthesis of the protein that the next stop be

recorded and a selenocysteine be put into the chain and protein synthesis continued.

Chappelle: What brought SBP2 gene defects to your attention?

Refetoff: As with all other instances, it started by an observation of a defect in the thyroid. In this instance, the first family identified by the Sudanese pediatric endocrinologist, Mohamed Abdullah, were children from Saudi Arabia, who were brought to our attention because one of them had a growth problem. Testing showed no growth hormone abnormality, but instead a very high level of thyroxine, T<sub>4</sub>, but *not* the active hormone, T<sub>3</sub>, which then suggested that they have a defect in the formation of the active hormone, and that maybe because of that the growth defect. There are three enzymes involved in the activation and metabolism of the precursor of thyroid hormone--T<sub>4</sub> into T<sub>3</sub>--and those are called deiodinases. So it was only logical to suspect the defect would be in one of the deiodinases. We looked at all three deiodinases and found no defect. Deiodinases are selenoproteins, so the next step was to do something to see what could be another possibility. We took skin biopsies from the individual, grew fibroblasts, and found that the activity of one of the deiodinases that is expressed in the fibroblasts--D2--was reduced. However, when we looked at the RNA, which is the gene transcription, it was normal. That is very simple to interpret: it means it is not a genetic defect in transcription, but in post-transcription, in the formation of the protein. And there are two possibilities: either the protein is being degraded rapidly, or it is being synthesized slowly--or less is being synthesized. What happened at that point is, what was to become a little bit of a "story" in the lab. I had to take a trip, and when I came back, my graduate student, Alexandra Dumitrescu, had found the mutation in the SBP2. So the story is, Refetoff leaves the lab and things happen, and maybe there is some truth to it. The way she proceeded was--because the family was big enough--she did a study of linkage or co-segregation and found she could exclude all the known enzymes that are involved in degradation, and she moved then to the enzymes involving synthesis, SBP2 being one--not an enzymes but involved in synthesis--and found that the three effected children were homozygous for markers in that gene and, therefore, it was a good candidate, and she found the mutation. As it happened, we had another family from Ireland that came to our attention only three months later, and would we have started with this family, we would have missed it because in this family they had two mutations: they were compound heterozygous. They inherited a different mutation from the father and a different one from the mother--the father being from Africa and so not related to the mother, where as the parents of the one from Saudi Arabia were related--were Bedouins. If we looked by co-segregation--looking if they were homozygous--we would have missed the defects because they have completely different mutations. But they had the same clinical phenotype, so it was logical--once finding one SBP2 defect to pursue the others.

Chappelle: Have you generated an animal model for this?

Refetoff: This is one of the projects I have. At this point Dr. Dumitrescu has already made the construct necessary for doing the mutations, and they are in stem cells ready to be injected in mouse eggs. One important issue that we know of is that if we completely knock out SBP2, the embryo doesn't survive. So the new mice that we are generating are a little bit more complex in the sense that they are *conditional* knockouts--that we can turn the gene off at different times of mouse development because we know that if it's turned off at conception, the mice won't develop. That will allow us to determine which selenoprotein is crucial for survival--that window that is necessary--and what kind of selenoprotein is required for that. So our work will go a little bit beyond the thyroid.

### **Thyroid hormone cell transporter, MCT8**

Chappelle: In addition to the three syndromes that you've been working on, you're also working on thyroid hormone cell transporter MCT8. What is the Allan-Herndon-Dudley syndrome?

Refetoff: This syndrome, first described by the three authors after whom the condition is named, was described in 1944 and was called X-linked mental retardation, and was within a large category of defects common in boys, and inherited through the X chromosome. It turns out that--in retrospect only--that the particular family that was first described has a mutation in the MCT8 gene, but not all boys with mental retardation have it the MCT8 gene mutation. And, as a matter of fact, recent studies that have systematically looked at boys with mental retardation have found that only a small proportion have this defect. What is typical to the MCT8 defects but not in other cases of mental retardation, is that they have a thyroid phenotype: they are always associated with a thyroid test's abnormalities. We believe that it is the thyroid abnormality that is causing the mental retardation. The thyroid abnormality is a high active hormone, T<sub>3</sub>, and a low inactive hormone, T<sub>4</sub>. And it is a bit of a surprise to have thyroid hormone deficiency when the level of active hormone is elevated. The defect is caused by the inability of this active hormone to penetrate the cell, especially the brain cells, thus causing thyroid hormone deficiency in the presence of high active thyroid hormone levels.

Chappelle: Are you using animal models for this?

Refetoff: Yes. So this has been actually the prototype--of what I have mentioned earlier--of that process of identifying a condition, linking it to a genetic defect, and trying through the mouse to characterize it in better form, and going back to the human. And in fact this is one condition where--through the mouse--we have been able to identify a thyroid hormone analog that despite the transport defect in the authentic hormone, can enter the cell because it does not require

that particular transporter as there are many other transporters. So this has been our model for future investigation of other defects.

Chappelle: What analog are you using?

Refetoff: It's an analog called DITPA, diiodothyropropionic acid. It has been used in the mice in which it has corrected the thyroid defect. It's not yet approved for use in humans in this country, but has been used outside the United States on a compassionate basis and has shown that it does correct the thyroid defects. Unfortunately, by the time the children that have received it were too old to correct the brain abnormality. Treatment has to be implemented very, very early to be effective.

Chappelle: How early?

Refetoff: Probably, before birth because some of the damage is probably caused *in utero* as the thyroid hormone that the mother provides cannot enter all the tissues of the embryo.

#### IV. ON COMPETITION IN SCIENCE

Chappelle: When you have been working on your research have you ever felt that you were in a race or a competition to get there first? Is that something that you've experienced?

Refetoff: Well, this is a very common phenomenon in scientific research. Sometimes these races turn out to be beneficial because they stimulate activity, but sometimes cause disagreements. There are many of them that I can think of and we all know of. From my own point of view, I've had two instances or actually three. The first one I just mentioned with Steven Usala, which has been a very happy and very productive competition, which has left no scars. The other one happened later with the recognition of TTF1--thyroid transcription factor 1 mutations, which is also associated with a neurological defect. In this case, Annette Grüters, who was the other laboratory--I mean it was in her laboratory that this mutation was also recognized. We got in touch and agreed to publish our findings, which were identical, in the same journal--in *JCI [Journal of Clinical Investigation]*. That was not the case with MCT8. And if you permit me, I have some notes so I don't say something wrong. [laughs]

The cases of MCT8 defects were brought--at least in my laboratory--to our attention by Knut Brockmann a neurologist from Göttingen, Germany, on March 15, 2002, and in May of the same year by a physician from Canada, Thomas Best. We received the blood samples from the two physicians in March twenty-first and July third of 2002; at which point, we started working on the deiodinases--as I mentioned earlier for SBP2--because of the discrepancy between the level of T<sub>4</sub> and T<sub>3</sub>. In this case, T<sub>4</sub> being low, T<sub>3</sub> being high--that

was a possibility. However, we didn't find any abnormalities in those deiodinases. So on September 8, I was in Gothenburg for the European Thyroid Association meeting, and I presented the cases to Josef Köhrle. It's kind of interesting because he is a co-author in the other paper I'm going to discuss. Josef is a very nice individual, a good friend. He suggested that there are two possibilities: either the children had iodine deficiency, in which case the  $T_3$  can be high because they reduced ability to add another iodine to the molecule; or that there may be a problem with thyroid hormone transport. Now, I don't know where he got that but certainly I should admit that that was his first suggestion among others. On October of that year, also at the ATA meeting Edith Friesema from Theo Visser's lab presented the discovery of the MCT8 gene in the rat. I was present, and said that I wasn't sure I believed it was a transporter because current dogma at the time was that the hormone--a small lipid soluble molecule--just got into the cell by itself. And so I asked her--"Did you find a mutation in humans to prove that this is in effect a functional transporter?" She didn't give me a positive answer. So in June of 2003, I learned that Theo Visser reported a mutation in MCT8 gene in the Endocrine Society meeting in Philadelphia. I was not at the presentation, and the next day I left for Italy. I wrote an e-mail on July 11, telling him that I learned that they found a mutation, and we found the same thing, and it would be nice if we published it in the same journal issue. He said that was a good idea but he had to consult with his co-authors--and I'm thinking, in retrospect, it makes sense because there were seventeen authors in that paper. July 24<sup>th</sup> he told me to wait. On August 22, he said that I have to wait a little bit longer because it was his vacation time, and he hasn't had the answers from his co-authors regarding co-publishing. On September 2<sup>nd</sup>, the co-authors could not reach an agreement and he sent me an e-mail saying that we should forget about co-publishing and that I should proceed as I wished. At that point, we sent our paper to *Human Genetics* and it was published December 5<sup>th</sup>, 2003, electronically, and then in January 5<sup>th</sup> 2004 it appeared in print. Now their paper was published later that year--I think it was October of that year--in *Lancet*. There was also another problem, which was related to the editors of the journal. We put a sentence in the manuscript saying that the results from Visser's "will be presented" at the September 2003 meeting of the American Thyroid Association--the results of Visser. However because our paper was published later--after the meeting--the editor changed the tense and said that the results "were presented." And that caused a little dispute between Visser and the journal.

Chappelle: Explain that again.

Refetoff: Okay. So in the original manuscript, we wrote that the result "will be presented" in the upcoming meeting of the American Thyroid Association. Now the American Thyroid Association occurred after submission of the manuscript--as we wrote it, but when the journal published the paper, it was five months later--the meeting had already occurred. So the editors changed the tense, saying that these results "were presented." Theo, then, had a long

discussion with the editors--I was not involved other than I received the copies of that discussion. The issue was that “were” would imply that we knew of their findings only after *their* results were presented at the ATA; whereas “*will be presented*” means that we knew *before*, which is true, and this is what we wrote at submission of our manuscript. The tense was changed because the editor felt it already happened and the date has changed. So an erratum was published. It’s an example, I think of the willingness that we all have to be the first and the willingness of recognition. Sometimes that becomes a little bit ridiculous. But anyway, this is my experience with that particular case.

Chappelle: How do you feel about that? What would you have done differently?

Refetoff: For me it’s not very important, and when I publish on the subject I always refer to our publication and theirs, and I don’t put any dates or any precedent who published first or who published after. But I think that for the young people it is very important, as there is a young person associated with each one of those publications. Their ability to recognize something novel, for the first time, as compared to finding the same finding that has been already found--is very different. And although it takes *years* to produce results, a few months of delay in publication may imply that the other person already knew about it. And I think that the tense used in the addendum of our publication recapitulates that point, which though a minimal thing for the editor who felt that the change accurate--in describing whether it was “will be” or “were”--it makes a difference for the author saying, did he/she know *before* of this finding, or not.

Chappelle: Is there more that you want to say regarding this issue?

Refetoff: As we become older and recognized in our work--what is our mission in helping young people get into science and be successful? And we have to be cognizant of these small things--mentioned above--that can be very hurtful to young people. There are other instances that have been debated, and I think the Endocrine Society may be able to do something about it. One is to protect the time of young people to do research when they are pressured--especially those in the medical profession--when they are pressured to be involved in patient care. What can the Endocrine Society do? It is probably through the grants that societies provide to young people that can have some influence on the institution to which the grants are given--to guarantee that the time is protected, the time used under those grants is protected. The other thing has to do with journals. Editors of journals want to achieve fame or want to improve the impact factor of their journals. The impact factor of journals is based on the number of quotations. One doesn’t have to be that bright to conclude that if a publication covers a field that is very popular or is used by many investigators the chances of the article being quoted multiple times is higher, irrespective of the importance of the article. So articles that deal with subjects with very narrow interest--even if they are excellent--are being overlooked because that would reduce the impact of the journal. I believe that editors should make an

effort to base their judgment and their acceptance of manuscripts for publication more on the quality and the importance of the work rather than on the effect it will have on the impact factor of the journal.

## **V. THE ENDOCRINE SOCIETY**

Chappelle: Speaking of the Endocrine Society, what has the Endocrine Society meant to you in terms of a community of scholars?

Refetoff: The Society has allowed me to interact with people that think differently--are in different areas of research--from whom I've greatly benefited. I think my research has always had a leap in progress when I encountered other people. Good examples are my sabbatical years during which I was involved in work different than that in my laboratory. So coming to the ENDO meetings I usually try to attend lectures that are not necessarily in my field in order to gain more knowledge, especially presentations that have technical importance to my work. I should admit that I have not contributed as much to the Society as the Society has given me. I have received several prizes from the Society, but I haven't been involved much in the politics and certainly not in any of the other administrative activities. And maybe there is a reason for that. I don't think that I'm that gifted in administration or in human relations, so the Society probably recognizes that, and kept me away.

## **VI. CURRENT VIEWS OF THYROIDOLOGY**

Chappelle: What are your current views of the field?

Refetoff: Of the field of the thyroid?

Chappelle: Yes.

Refetoff: Well, the problem of the thyroid and again, being my field I certainly have some bias regarding my interest. I think the thyroid field is very interesting from the point of view of biochemistry, from the point of view of anatomy, and various aspects of that particular gland compared to others. On the other hand, for many years it has been recognized that giving thyroid hormone can cure the majority of conditions associated with thyroid deficiency, and, therefore, it has not elicited as much interest from the government, from NIH, or from other funding bodies because there is no need for sophisticated drug development--very complicated treatments--like is the case with diabetes or other conditions. I think that the few conditions I discussed that are unique--where thyroid hormone cannot solve the problem--are a little bit in the realm of those of diabetes, but they are few and far between, and that's one reason the thyroid research has not received as generous funding as other areas of endocrinology. So I would like to see more recognition in thyroid research with respect of knowledge gained in basic sciences and

understanding how hormones work, rather than just centering on the necessity to do research in order to cure thyroid diseases.

Chappelle: Thank you.

Refetoff: You're welcome.

[End of Interview]

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**Interview History—Samuel Refetoff, MD**

Dr. Refetoff was interviewed by Michael Chappelle on June 4, 2011, during the Endocrine Society's Annual Meeting held at the Boston Convention and Exhibition Center in Boston, Massachusetts. The interview took place in a conference room at the Westin Hotel and lasted sixty minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Refetoff prior to its accession by the Oral History of Endocrinology Collection. The videotape and transcript are in the public domain, by agreement with the oral author. *The original recording, consisting of two (2) 45-minute mini DV cam tapes, is in the Library holdings and is available under the regulations governing the use of permanent noncurrent records.* Records relating to the interview are located in the offices of the Clark Sawin Library's Oral History of Endocrinology Project.