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ROGER H. UNGER, MD

Interview conducted by
Adolph Friedman, MD
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FAMILY BACKGROUND AND EDUCATION

Dr. Friedman: Dr. Unger, am I doing this with your permission?

Dr. Unger: Yes you are.

Father's career: developed the first direct transfusion instrument, started the first blood bank in New York, and started the blood bank for the French during WWII

Dr. Friedman: Dr. Unger, I understand you were born on March 7, 1924, in New York City. Please tell me a little bit about your parents.

Dr. Unger: My father was a physician. When he was an intern, he developed the first direct transfusion instrument. He was a well-known hematologist. Subsequently, when direct transfusion became obsolete, he started the first blood bank in New York. I remember as a child seeing him do direct blood transfusions in the operating room. It was like a surgical procedure--a real big deal. So it was quite a technological change to see corpsmen in the military doing transfusions as though it was nothing. It was a major transformation that really happened without much fanfare. Then during World War II, he was sent by President Roosevelt to examine the Russian cadaver blood banks. They used cadaver blood. He came back to New York with the information and was violently opposed by Cardinal Hayes and was dropped, but he started the blood bank for the French--for DeGaulle--during the war.

Dr. Friedman: Did your mother have a profession?

Dr. Unger: No, she was a housewife.

Dr. Friedman: Did you have any siblings?

Dr. Unger: I have a brother seven years younger than myself.

Dr. Friedman: What does he do?

Dr. Unger: He had been a journalist; then he retired and became a surprisingly successful biographer of early American individuals such as Noah Webster and John Hancock. He lives in New York half the time, and in Paris half the time.

Dr. Friedman: When did you get married?

Dr. Unger: I've been married twice. I got married in 1946, had three children who are grown, and I got married again in 1984, and I have one younger child by that marriage.

Dr. Friedman: Tell me what your children do.

Dr. Unger: I have one son who is a pediatrician; one son who is a journalist--who had been editor of the *Boston Magazine*--and who is now director of a dot-com company in New York. He just started the job, and I've forgotten the name of the company, but it's a major company. I have a daughter, who is a housewife.

Dr. Friedman: Please tell me about your lower school education. Was it public, private?

Dr. Unger: It was all private. I went to Horace Mann School in New York until I was about fifteen years old; then I went to Taft School in Watertown, Connecticut--from which I was graduated in 1944--and went to Yale. I was in the military for a while at Yale, and then went to the College of Physicians and Surgeons of Columbia University.

Dr. Friedman: In your earlier days, was there anybody in your grammar school or high school training or college that influenced you to go into medicine? Of course, being the son of a physician, you obviously were influenced by the surroundings to go into medicine.

Dr. Unger: No, there was no one at all. My father's two brothers were also physicians, and his uncle--my great uncle--was also a physician, so it was heavily weighted towards medicine.

BELLEVUE HOSPITAL

Dr. Friedman: You have a great background. You subsequently went to Bellevue. Was there anybody that you met at Bellevue who influenced your research choice of activity?

Dr. Unger: Not really. The people that stand out in my mind were Dickerson Richards and Andrea Cournand--shared the Nobel Prize--but they were cardiologists and pulmonologists, respectively. In terms of their brilliance, they influenced me; but they didn't influence me as far as my choice of scientific specialty.

ARMY SPECIALIZED TRAINING PROGRAM (ASTP); PUBLIC HEALTH SERVICE ASSIGNMENT TO A DIABETES DETECTION DRIVE IN DALLAS

Dr. Friedman: What was your military experience?

Dr. Unger: Well, I'd been in the ASTP (Army Specialized Training Program) from my entry into medical school--which was in 1944--and when I graduated in 1947, the war had ended, and I was discharged. But I still didn't have enough time to pay back for the ASTP, so I had to go back once again. In 1951, I went into the Public Health Service and was sent to Dallas, and that's how I got to Dallas.

Dr. Friedman: What did you do in Dallas?

Dr. Unger: I was director of a diabetes detection drive, which had been organized by Hugh Wilkerson, and that's how I got into diabetes, basically.

Dr. Friedman: What kind of private practice did you have in New York, and why did you give it up?

PRIVATE PRACTICE IN NEW YORK CITY; DECIDING ON THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL, DALLAS

Dr. Unger: When I was discharged from the Public Health Service, I was undecided whether to go into practice or research. While I was in Dallas, the University of Texas Southwestern Medical School was just being organized and was in shacks--in Quonset huts. When I was stationed there, I was looking for the medical school because I wanted to make rounds to try and keep up my clinical skills, and I went into these huts and asked where the medical school was. It was actually Jean Wilson--although I didn't know that at the time--said, "This is the medical school." While I was there, I had some exposure to the embryo faculty; and I was very impressed even though the facilities were a joke. These were just young guys. There was a whole group of very young, brilliant people that I thought would someday make it a great school. I had no idea we'd pick four Nobel laureates within thirty years. I knew it was destined for something better. My term ended there, and I was faced with a decision. I had a family, and my father wanted me to come back to New York and open an office, and I did. It was on 53rd Street and Park Avenue, where the Seagram Building now stands. After I established my office and was just about to break even in my practice, I got an eviction notice that they were going to build the Seagram Building on my site and I would have to relocate. Since I was vacillating between practice--which I liked--and research--which I really had not done, I decided to see if there was an opening in Dallas. There was, so I took it. Rather than relocate the office and start over, I moved back to Dallas.

Dr. Friedman: When you went to Dallas under whom did you start to work?

Internal medicine at the Dallas VA Hospital

Dr. Unger: I started working at the Veterans Hospital in internal medicine.

Switch from gastroenterology to metabolism

Dr. Friedman: What diverted your interest from GI to metabolism?

Dr. Unger: Well I was never interested in GI, but that was the only opening title that was available, so I was called a GI. I didn't see patients or have anything to do with gastroenterology. It was just a title.

INVESTIGATING INSULIN AFFECT, SULFONYLUREAS, AND DIABETIC DIAGNOSTICS

Dr. Friedman: Almost simultaneously with your changing interests, you were already publishing one of your investigations of insulin affect, sulfonylureas, and diagnostic tests

for diabetes, which you continued to work on. Was there anything particularly that switched you over and influenced you into diabetes at that time?

Discovering inapplicability of diagnostic standards for diabetes

Dr. Unger: Well, I had been the director of a diabetes detection unit in 1951 when I was in the Public Health Service, and my job then was to apply the standards for diagnosis for about 125,000 people in the city of Dallas. I soon learned that those standards were absolutely wrong, because if I applied them about twenty-five percent of the people in the city would be diabetic. In other words, they were much too sensitive. I became interested in trying to analyze and make the standards for the diagnosis more realistic, and that's how I got into the intravenous tolbutamide tests. Having done that, I became interested in mechanism of sulfonylureas action, and--one thing led to another--and I became more deeply involved.

GLUCAGON ANTIBODIES; DEVELOPING AN IMMUNOASSAY Berson doubts a radioimmunoassay for glucagon can be developed

Dr. Friedman: The first change in the trend of your work, which occurred about 1959 to 1960, was a study of glucagon antibodies and immunoassay for glucagon. Your work on glucagon was very extensive. Please tell me about it.

Dr. Unger: I was convinced that the future of diabetes lay in the ability to assay the glucoregulatory hormones, of which only insulin was recognized at the time. The first immunoassay employed insulin-labeled red cells, which was developed by Stavitsky and Arquilla in 1950. About that time, insulin labeled with I-131 was being used by two groups, one of which was Sol Berson's. I had the idea that, rather than label the insulin with a red cell, you could get much better sensitivity labeling it with radioiodine. So I called him up and asked if he could show me how to do that. He wanted to know why I wanted to do that, and I told him. He said, "Can you come up and see me?" I said yes, and I did. It turned out that he was already well on his way to having developed a radioimmunoassay for insulin. He showed me the data, and I said to him, "Well, since you've done insulin, why don't I just go ahead and do RIA for glucagon?" He said, "Well, you're welcome to try, but I can tell you that it won't work, because we've tried and failed." To make a long story short, he showed me how to iodinate the glucagon. We had been immunizing rabbits and found that we did have glucagon antibodies and that we could make an RIA for glucagon. When I called him up to tell him, he was very pleased and congratulated me. He gave me permission to publish our results from the glucagon assay--and they appeared in 1959--even though he had not as yet published his insulin assay. In other words, he was being extremely generous and, of course, I acknowledged his priority in our paper. His insulin RIA paper did not get published until 1960. He got all of the recognition that he deserved--he and Roz Yalow--since the Nobel Prize was awarded for that work.

KETONES: MECHANISM AND FEEDBACK LOOPS

Dr. Friedman: I was unaware of the stimulatory feedback of the ketones on the beta cells. Would you mind telling me a little about that?

Dr. Unger: As you know, one of insulin's major actions is to inhibit the release of free fatty acids. Normally free fatty acids come out when you're starving, exercising, or fasting--not when you're feeding. When fatty acids come out of the fat cells, they go to the liver and they're oxidized to form ketones. You would not want that to happen if you're well fed. When ketones go up in the blood, they stimulate insulin that reduces the fatty acid levels and prevents you from going into ketoacidosis when you're fasting. If you're a diabetic, you have no insulin; then there's a strain ketogenesis because you don't have this feedback. The feedback makes the difference between starvation ketosis and diabetic ketoacidosis.

Dr. Friedman: Thank you. In 1965, you worked with high growth hormone levels in ketoacidosis. I think that was prior to Jesse Roth's work on growth hormone and blood sugar. Please explain to me whether or not I'm mistaking.

Dr. Unger: I'm not sure about the priority. It was just a chance observation. I don't think it was a very significant one.

Dr. Friedman: When were you visiting Berson and Yalow in relationship to when Jesse was there? You said you were there when Bauman and Rothschild were there, which was three or four years before Jesse got there.

SPEAKER AT THE NOBEL SYMPOSIUM

Dr. Unger: I was there in about 1956 or 1957.

Dr. Friedman: In 1970, you worked on gastrointestinal hormones as modifiers of islet cell secretion at the Nobel Symposium in Stockholm. How did you get to the Nobel Symposium?

Dr. Unger: I was invited.

Dr. Friedman: Were you invited as a speaker, or to support somebody?

Dr. Unger: As a speaker.

Dr. Friedman: Not to support somebody else.

Dr. Unger: No. They put on a symposium all year long on different topics.

GLUCAGON-INSULIN RATIO

Dr. Friedman: In 1970 and 1971, you wrote several articles on the glucagon-insulin ratio and the effect of endogenous glucagon and glucagon immunoreactivity on insulin secretion. Would you please discuss that with me--also, the effect of various chemicals and diet and insulin on glucagon secretion?

Dr. Unger: The whole metabolic status of anybody--animals, humans--is determined by the relative concentration of insulin to glucagon; that is to say, whether you miss your inner anabolic mode, you're making macromolecules. You're eating, and they're being converted into proteins, fats, glycogen. On the other hand, if you're starving or have a severe chronic illness, quite the opposite is happening. You're breaking down these macromolecules. Glycogen is converting to glucose, triglycerides are going to fatty acids and ketones, and proteins are being broken down to amino acids. If you're in an anabolic mode, you have a high insulin ratio. If you're in a catabolic mode, you have a low insulin-glucagon ratio. That's what determines it.

Glucagon synthesis and secretion

Dr. Friedman: What percentage of the glucagon secretion in the body comes from other parts of the GI tract than the pancreas? Are there A-cells elsewhere in the stomach and gut?

Islet physiology

Dr. Unger: They are the true alpha cells. You have to remember that the gene that encodes glucagon is a complex gene that makes other glucagon-like molecules--the same gene--and the difference in the end product depends on whether the cell has the enzyme that can feed the precursor into the final form. The alpha cells of the islet have that machinery to produce true glucagon. There are alpha-like cells, known as "L" cells, in the gastrointestinal tract that have the same gene, but they lack the machinery to make true glucagon. There is an exception to that. There are some cells in the stomach that under some circumstances can make true glucagons as well. You see this mostly in totally depancreatized individuals. Some glucagon is produced in the stomach. It's a very small amount. We found that about fifty percent of insulin is picked up on the circulation through the liver, but that was Leonard's work more than mine.

Dr. Friedman: The glucagon traveled with it. In other words, the difference between the novo-insulin and pig or cow insulin, was that they carry glucagon with them and the novo did not.

Dr. Unger: I don't remember, but I know one of them has glucagon. Glucagon was not recognized to be a hormone when I got into the field.

Dr. Friedman: Did Wylie Vale work with you in 1977/1978, or was he only there with you on a visiting fellowship?

Dr. Unger: No, he never worked with me. We've never worked together. Why?

Dr. Friedman: Because you had some coauthored stuff.

Dr. Unger: He sent us some somatostatin.

Dr. Friedman: But you never worked with him.

Dr. Unger: No, we never worked together.

Somatostatin: a valuable experimental tool

Dr. Friedman: What was the role of somatostatin in gastric acid secretion, insulin and glucagon secretion. Where does the somatostatin fit in?

Dr. Unger: The somatostatin proved to be a valuable experimental tool, because you could manipulate the release of the islet hormones at a time when there were no such things as knockouts to do experimental maneuvers. As far as the physiological role of the somatostatin--it is located in the islets--I think it's minimal. It wouldn't be there if it wasn't doing something, [but] whatever it does is not sufficient to register using the techniques that we have. The only way you could answer that is to do a tissue specific somatostatin knockout. In theory, it may have a dampening effect--a tonic restraining effect on the level of secretion by the other hormones--but that's just theory--but can be proven by the techniques that we have available right now. As far as gastrointestinal somatostatin, there may be a feedback in which the local somatostatin inhibits HCL secretion when it gets too high. But that too is speculation. As far as the somatostatin in the central nervous system, that's a growth hormone release and inhibitor.

CALORIC RESTRICTION AND TYPE 2 DIABETES

Dr. Friedman: Why is there a diminishing effect of caloric restriction on the control of hyperglycemia in diabetics--assuming there's no change in their hormonal state and exercise?

Dr. Unger: Which kind of diabetes are we talking about, because I'm not aware that there is such a thing?

Dr. Friedman: Well, you did write on the diminishing affect of caloric restriction on the control of hyperglycemia. It can only be type 1 or type 2.

Dr. Unger: Caloric restriction is very effective in type 2. Wait; let me see this paper. The glucagon goes up, and this is probably in relation to that; but in type 2 diabetes that's not true because you can restrict calories--you will be able to reverse the diabetes.

Dr. Friedman: What is the mechanism of the impaired glucose transport and the causation of hyperglycemia?

Dr. Unger: What is the mechanism? That is such a complex field, and it's now in a state of revolution. I've never been involved in that area at all, so I'd rather not comment. The recent work of Saltiel--that's a whole huge field that I've never had anything to do with.

THE PHYSIOLOGIC ROLE OF LEPTIN

Dr. Friedman: What's the overall role or effect of leptin in preventing diabetes, and how does it work? Is triglyceride depletion the whole answer?

Dr. Unger: Well, the kind of diabetes we're talking about is obesity related. What our work has shown is that the physiologic role of leptin is to allow you to overeat and get fat without damaging tissues, such as the islets and heart, the skeletal muscles, and the liver. When you don't have leptin action, if you have the caloric excess, the triglycerides will be distributed throughout the body; and when that happens, they enter pathways that can destroy themselves. Namely, they can enter the ceramide pathway and that induces the enzyme that produces nitric oxide, and that causes apoptosis of the islet cells, the heart, skeletal muscles or any tissue. The islets are the most vulnerable, because with the muscle, you can exercise away the excess if you're vigorous. The liver can secrete the excess as BLDL(??), but what gets into the islets is trapped, and that's why they get destroyed first.

Dr. Friedman: How does the hypothalamic action of leptin in hyperlipemia work?

Dr. Unger: Leptin works in the hypothalamus in normal people. The blood brain barrier threshold to leptin is the level of between 8 and 15 nanograms per millilitre. In obesity, you go way above that threshold, so that you're not getting much of a hypothalamic affect. Obviously, if left and it prevented obesity, we wouldn't have fifty-five percent of the population over weight. Obesity has been rampant only for about fifty years. It's not time enough to evolve any obesity system. The problem that life on this planet has faced is not obesity--it's starvation. Obesity is a mechanism to overcome starvation. You can survive a lot longer if you're obese than if you're skinny. There's a natural selection for obesity, not against it. What leptin does is permit you to become obese without injuring the other cells of the body. The only cells that are adapted to store fat are the adipocytes. The non-adipocytes are not adaptable, and they get injured if they are over loaded.

Dr. Friedman: In other words, what you just said is a relative explanation of leptin resistance in the lipid abnormalities of aging.

Dr. Unger: Yes.

Dr. Friedman: Will you remember to send me a *FASEB Journal* of 2001?

Dr. Unger: I can try to remember, but you might just fax a request to my secretary and she will send it.

Dr. Friedman: You wrote a couple of articles or chapters with Norby Freinkel. How did you happen to get together--with him being in Chicago and you being in Texas?

Dr. Unger: Well, that's no deterrent; my closest collaborator is in Geneva, Switzerland. I'd forgotten that Norby was interested in pregnancy; he wanted to do glucagon assays, so we did it for him. We did a service for him; we never really collaborated with him. And he put our name on the paper.

AWARDS AND HONORS; ENDOCRINE SOCIETY SERVICE

Dr. Friedman: You've received many noteworthy awards and honors in the past twenty years with your work in diabetes, including the eleventh most cited author in the field of diabetes and endocrinology from 1961 through 1976. This includes French, Belgium, Swiss, and Canadian awards as well as the Koch Award from the Endocrine Society. That's a terrific achievement. Speaking of the Endocrine Society, you were on the editorial board of *Endocrine Reviews*, 1987-1991 [and] *Endocrinology*, 1977-1982. Now, I know you're active in many editorial boards for other societies--like diabetes, physiology and so forth--but did you do anything else for the Endocrine Society? Were you on any committees or on the council?

Dr. Unger: No.

Dr. Friedman: Of your fellows and associates or your co-workers, which of them went on to head their own laboratories or their own departments?

FELLOWS, ASSOCIATES, AND CO-WORKERS

Dr. Unger: Madison was a professor of medicine, and I worked for him; he didn't work for me. Eisentraut is a technician. Valverde was a fellow, who has her own lab in Spain. Orci has been my closest collaborator. He's chairman of the Department of Morphology at the University of Geneva for the past thirty years. Figierra, I don't know what happened to him. How did you happen to pick these? I had about fifty postdocs.

Dr. Friedman: Because I think they were the most frequent or the most numerous of your coauthors, but you can correct me because, after all, that's why we're here.

Dr. Unger: Ohneda--I had both the father and son. Akira Ohneda was a fellow of mine in 1969; then, in about 1990, his son came to my lab, so I had two generations of Ohnedas. Albert Renaud was a colleague and a friend.

Friedman: He's in France isn't he?

Dr. Unger: No, in Geneva. When I took my sabbatical in Geneva, I spent a considerable time with him. Marvin Siperstein was on the faculty with me, and a close friend.

Dr. Friedman: Jean Wilson mentioned Siperstein too.

IDENTIFICATION OF GLUCAGON AS A TRUE HORMONE

Dr. Unger: Yes, he was a very beloved colleague for all of us. The major work of my career, you haven't mentioned; and that was identification of glucagon as a true hormone.

Dr. Friedman: Please discuss that with me.

Dr. Unger: Part of that is considered a contaminant of the insulin extraction procedure. We identified it specifically localized in the alpha cells, and we worked out its hormonal role in glucoregulation. Then we established that you couldn't get diabetic ketoacidosis in the absence of glucagon. In other words, insulin deficiency by itself would not cause diabetic ketoacidosis. What happens is, when you have insulin deficiency, glucagon goes very high, and it's the high glucagon that causes the liver to empty itself of glycogen and to produce ketones. If you take out all the beta cells but also take out all the alpha cells, so you have a bi-hormonal deficiency, which you will have with a normal glucose, provided you don't eat. If you eat, of course, your glucose will go up. But you don't get the endogenous hyperglycemia or the increased ketogenesis that you would otherwise get. Normally, when you have an insulin deficiency, your glucose goes sky high.

Dr. Friedman: They sort of nullify each other.

The Banting Medal; introduction into the National Academy of Sciences

Dr. Unger: The role of insulin on the liver is to nullify the action of glucagon. If you don't have any glucagon, insulin has nothing to do in the liver. It still has plenty to do outside the liver, but its role on the liver requires this to oppose the actual glucagon. That's what I got the Banting Medal for and [why I] got into the National Academy of Sciences. That was the work.

Dr. Friedman: You told me at dinner that you were doing that for the last ten years.

Dr. Unger: Doing what?

Dr. Friedman: This new work.

Dr. Unger: Yes, that was all finished. In the 1980s was our last glucagon paper.

Dr. Friedman: Is there anything else you think I should know about you, or I should have asked you? Or, on the other hand, is there anything that you would like to tell me about your work and career?

ENTEROINSULAR AXIS

Dr. Unger: I think the enteroinsular axis was an important observation, because that's about as close to gastroenterology as we got. It established the fact that, when you eat something, you send out messages from your intestine to your islets, so that they know what you've been eating, and they know what is about to be absorbed. Instead of waiting until the last minute in reacting, they're prepared to meet the incoming meal with an appropriate production of hormones that will direct the assimilation of whatever it is that you've eaten.

FATTY HEART

Dr. Friedman: You mean insulin?

Dr. Unger: Insulin and glucagon. If you eat steak and potatoes together, all you need is insulin. Let's say you're carnivorous; you don't need any potatoes, and you just eat the steak: insulin is going to come up so that you can metabolize the amino acids in the protein, but you will get hypoglycemic. If you eat steak with no potatoes, insulin will come up and the glucagon will go up with it. That will cover the insulin just like if you're doing an insulin IV; you would want to cover it with some glucose so that you wouldn't get hypoglycemic, right? The most exciting stuff that we're doing right now is that we think that the most common form of heart disease in the United States today--may not be endocrinology or cardiology--is unrecognized. It's completely ignored. It's as common as coronary artery disease.

Dr. Friedman: Which is what?

Dr. Unger: It's actually a disease which was first described in 1628 by William Harbor and has been recognized consistently up until the past sixty or seventy years. That's a "fatty heart." If you look at the heart in obese humans--you can do Oil Red O staining--and you will find, as it turns out, that there is a remarkable correlation between the body mass index and the amount of intracardiomyocyte lipids. If you have too much fat in a non-adipocyte, you will lose it. It will die of apoptosis. Once you've lost a heart cell, it's gone. You cannot regenerate it. It's a terminal cell. Over the years if you are obese, you're losing--very slowly--one heart cell after another; at the end of twenty or thirty years, you're not playing with a full deck of cardiomyocytes. So that we think this is a major factor in the loss of cardiac function. It occurs with aging although it's exaggerated in obese people at a much earlier age. And it's completely preventable, but it's not recognized.

Dr. Friedman: Is it correctable?

Dr. Unger: Yes. You can correct it either by diet, which would be the most rational way, or using one of the glitazones, like rosiglitazone. What rosiglitazone does is mobilize fat out of the non-adipose tissues, and even though you get heavier because the fat is going into your adipocytes, that is where fat belongs. It doesn't belong in your heart, your beta

cells, and doesn't belong in your skeletal muscle. So if you're exercising, this is probably nothing that you have to worry about, because you exercise and seem to be in very good shape. But if you're overeating and not exercising--it has been known for years that animals and humans that eat less can live longer. What's new is the fact that more than half of the population is overweight. No clinical cardiologist that I know of today will make a diagnosis of a fatty heart, even though this is a common diagnosis going back to the seventeenth century. In the eighteenth and nineteenth century, nephrologists used to drop the heart into a bucket of water to see if it floats. Today we do sophisticated MRI's to pick this up noninvasively. In obese rats with lipid in the heart, we put them on troglitazone to get rid of the lipids, and guess what happens to their cardiomyopathy? It disappears! Let me rephrase that. We cannot reverse it once it's there. You can prevent it before it's there by treating it with troglitazone.

Dr. Friedman: It can also be prevented from going any further.

Dr. Unger: That's right, but once the cell is gone, it's gone; and there's no way of getting it back, other than a cardiac transplant. So the idea is to prevent the loss of these cells. This is what I'm presenting tomorrow at the NIH.

Dr. Friedman: Well, thank you very much for your time and your patience.

Dr. Unger: Well I've enjoyed the interview, I admire what you're doing, and I very much liked the dinner.

Dr. Friedman: My pleasure.

Dr. Unger: I will tell your old friends that I met you, and I'm sure they will be pleased.

Dr. Friedman: Thank you.

End of Interview

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