A Grain of Truth: The Gluten Summit
Presenter: Yehuda Shoenfeld, MD, FRCP

Are You Developing an Autoimmune Disease Years Before Symptoms?

Dr. O'Bryan: Hello, everyone! Welcome to another edition of A Grain of Truth: The Gluten eSummit. And it is my distinct pleasure and honor to be interviewing one of the world's greats today, Dr. Yehuda Shoenfeld.

Dr. Shoenfeld is the founder and director of the Zabludowicz Center for Autoimmune Diseases at the Sheba Medical Center, which is affiliated to the Sackler Faculty of Medicine in Tel Aviv University, Israel. And, we're speaking to Dr. Shoenfeld in Israel today.

Dr. Shoenfeld is the incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at the Tel Aviv University. His clinical and scientific works focuses on autoimmune and rheumatic diseases. And he has published more than 1,700 papers in journals such as the *New England Journal of Medicine, Nature, The Lancet,* the *Proceedings of the National Academy of Sciences of the United States,* the *Journal of Clinical Investigation,* the *Journal of Immunology,* the journal *Blood,* the Journal of the *Federation of American Societies for Experimental Biology,* the *Journal of Experimental Medicine, Circulation, Cancer*, and many, many others. His articles have had over 31,000 citations. What that means is that when other researchers publish their work, they use Dr. Shoenfeld's work as their references.

He has written more than 350 chapters in books, and has authored and edited 25 books, some of which have become cornerstones in science and clinical practice, including the *The Mosaic of Autoimmunity*, *Infections and Autoimmunity*, and the textbooks *Autoantibodies* and *Diagnostic Criteria of Autoimmune Diseases*. He is on the editorial board of 43 journals in the fields of rheumatology and autoimmunity, and is the founder and editor of the *Israel Medical Association Journal*, the representative journal of science and medicine in the English language in Israel.

He is also the founder and editor of *Autoimmunity Reviews* and coeditor of the *Journal of Autoimmunity*. For the last 20 years, Dr. Shoenfeld has been the editor of the *Journal of Medicine* in Hebrew, *Harefuah*, which is the journal of the Israel Medical Association. And he has edited **[2:30]** the Israel medical encyclopedia. He has organized over 20 international congresses in autoimmunity where doctors come from all over the world to share ideas.

In 2005, Dr. Shoenfeld received the European League Against Rheumatism prize in Vienna for "The Infectious Etiology of Antiphospholipid Syndrome". He has received a gold medal from the Slovak Society of Physicians for his contribution to Israeli/Slovak collaborations. And he's an honorary member of the Hungarian Association of Rheumatology.

In 2008 he received the Nelson's Prize for Humanity and Science from the University of California, Davis. In 2009 he was honored as Doctoris Honoris Causa from Debrecen University in Hungary. And since 2009, he has been an honorary member of the Slovenian National Academy of Sciences. In 2012 he was awarded a Life Contribution prize in Internal Medicine in Israel. He has educated a long list of students, over 25 students, who now hold heads of departments and institutes in medical research.

So obviously we have the world's authority here on autoimmunity. And Dr. Shoenfeld, thank you so much for joining us today!

Dr. Shoenfeld: Thank you very much! And I appreciate your introduction. I'm sorry that my parents cannot hear it because my father would have been proud of me. And my mother would have believed what you dictated.

Dr. O'Bryan: I fully understand what you're saying. And I'm sure they're hearing it at some level from somewhere.

Can we begin, Dr. Shoenfeld, with some basic questions? We know that there are many thousands of doctors listening to this interview, and many tens of thousands of the general public. So, for the general public's point of view, can you tell us first what is the immune system in our body? And what's the purpose of our immune system?

Dr. Shoenfeld: The immune system is one of the most interesting systems in the body, not to say that some others are not interesting. But if you would go over the Nobel Prize laureates in the last 20 to 25 years, most of them were given and granted to revelation of the immune system. And it seems **[5:00]** that in the future we will be able even to manipulate from outside the immune system in such a way that we cannot imagine even today.

The immune system is constructed of at least two arms, which are called the cellular arm and the humoral arm. The humoral arm are actually missiles, which are Y-shaped. And they are targeted against foreign invaders. The cellular immune system, the cells themselves which invade the tissue, and they fight for instance, ulcers as well as cysts, which have been turned into malignant cells.

So, these two arms are extremely important. They are directed to prevent foreign invaders. This reminds me very much of an Army, which the aim of the Army is to protect from, let's say terrorists to invade the territory of the country. Now by and large the immune system is working very well when the system is mature. Not necessarily in infants until the age of four or five. And therefore infants are subject to more to infections than adult people.

The same happens when we age and the immune system ages. And then we find more infections in the elderly. But, in between, we are supposed to be protected from foreign invaders. Yet it's a constant war between the invaders, viruses, bacteria, and parasites, and the immune system in which each one of the fighters try to overcome the other. And therefore, despite having an immune system, we do get pneumonias, gastroenteritis, and so forth.

Today, we will concentrate not on the ability of the immune system to attack foreign invaders like viruses and bacteria, **[7:30]** but when the system goes awry and attacks our own tissues—which we refer to as friendly fire or shooting our own tissue and organs—and to explain how the immune system is really deranged and does not recognize anymore our own tissue as our own, and attacks it like it was a foreign invader.

So the basic term that we will use is "tolerance" because, by and large, the immune system should not attack our own tissues and cells and organs. But when we lose the tolerance, then your system may attack any organ in our body. Having the two arms of the immune system—the humoral immune system and the cellular immune system—may explain why we have the 80 different autoimmune diseases being classified to those who are being attacked by the missiles, the humoral-mediated autoimmune diseases, and to cellular-mediated autoimmune diseases.

Classical diseases, lupus, systemic lupus erythematosus, which is a humoral-mediated autoimmune disease, while cellular autoimmune disease may be regarded, for instance multiple sclerosis, as an autoimmune disease in which the cells invade the brain and attack our own neurological cells in the brain. So these are the basics of immunology and why we develop autoimmune diseases, or what are the autoimmune diseases.

Dr. O'Bryan: Thank you for that explanation. And for our general public listening audience, the importance of knowing the different types of immune functions we have, both humoral and cellular, is that our doctors will be recommending different approaches depending on which one is more active for you. There's a lot of crossover, but sometimes it's really good to know which branch of the immune system you're wanting to address.

Dr. Shoenfeld: You're absolutely right! Let's suppose that you have a **[10:00]** humoral-mediated autoimmune disease. So the therapy approach will be to clean or to take out those missiles which attack our own body. Just to give an example, there is a therapeutic system called plasmapheresis, which means to clean the plasma from the longer missiles, which we will refer to them from now on as autoantibodies, meaning attacking our own tissues.

So, this plasmapheresis, cleaning the plasma, the fluid of the body, will not help in those cases in which we have an effect by the cells of the immune system. And, in those cases, we will have to use either drugs, which are aimed to destroy these attacking cells, called immunosuppressive therapy or cytotoxic therapy, and/or using what we nowadays have, a more specific attack on the cells by anti-missiles, which are called biological drugs. So basically, the classification of the cells may determine eventually the way of therapy in the specific autoimmune condition.

Dr. O'Bryan: Yes. You referenced lupus as an example of a humoral autoimmune disease. I'd like to go right into your area, one of your areas of expertise where you are the renowned world's expert. That is the world of predictive autoimmunity. In 2003 in the *New England Journal of Medicine*, Melissa Arbuckle published a study where she looked at 130 patients who were in the VA Hospital system who had been diagnosed with lupus. If they're in the VA system, they're veterans. If they're veterans, they were in the Armed Forces. If they were in the Armed Forces, they had their blood drawn many times **[12:30]** over the years when they were healthy Navy sailors or Air Force personnel.

Perhaps there was a staph outbreak on the base, and you felt tired. So you went and got your blood drawn and they said, "No, you don't have staph. Go back to work. You're fine." The government has been saving all of that blood since 1978, here in the United States. They have tens of millions of samples of frozen blood.

So Dr. Arbuckle went back to the VA for these 132 patients currently diagnosed with lupus and asked for permission to look at their blood samples that were frozen from when they were healthy many, many years ago. What she found was that 115 out of those 130 patients had elevated levels of these missiles—these autoantibodies—to their own tissue for lupus. There are seven antibodies that have been identified for lupus.

And she found that all of them continued elevating. The average was nine years before there were any symptoms. They had elevated antibodies that were measurable, and each one of these seven kept going up every year. A little bit, some, a lot at once, and then some, a little, and then a lot later, until they plateaued. Then the symptoms came. Then six months to two years later, they got the diagnosis of lupus. So the question they

came up with was, “When did they get lupus?” And our position has been as clinicians, the mechanism began many, many years before the symptoms ever showed.

Is that the rationale for this world of predictive autoimmunity, to begin to identify these antibodies long before there are symptoms that have developed?

Dr. Shoenfeld: You have summarized it precisely. What you said has several consequences and take-home messages. Number one is that autoimmune diseases have a long incubation time. There was this wonderful article in the well-known journal called the *New England Journal of Medicine* in which it has been found that the markers, as well as those missiles—the autoantibodies—have been detected **[15:00]** in the blood of the patients years before the disease becomes overt clinically, the patient had, indeed, symptoms of either pains in their joints, fever, or increase in the organs due to inflammation and so forth. Sometimes the incubation time may take even 40 years.

We have an autoimmune disease called primary biliary cirrhosis. The disease affects women 20 times more than men, like many of the autoimmune diseases which are more prevalent among females. However, the diseases do appear—and it’s frequent—at the sixth and even seventh decade. Yet the marker, the same autoantibody, the missile, that is so specific that if you detect it incidentally, even 20 or 30 years ago, you can assure the younger woman that when she will reach the age of 60 or 70, she will develop this devastating condition called primary biliary cirrhosis.

So it means that you need to have the missiles, the autoantibodies, in the blood for a long time before the damage accumulates in such a way that the disease becomes overt. This is called prediction of autoimmunity. In the past, when students have asked me, “What would you do with a completely healthy subject in which you found such antibodies or autoantibodies like anti-DNA antibodies?” Or let’s say for the sake of primary biliary cirrhosis, what is called anti-PBH antibodies. I would have said, “Leave the healthy subject alone. We treat patients. But we don’t treat inflammation of the lab, laboratoritis.”

Yet what we have learned is that today we should not neglect this incidental finding. And we should follow the patient for a long time because those who have this marker in their blood, they have a greater **[17:30]** chance to develop a clinical disease. Prediction is important, but it has meaning only if you can help the patient. The question is even ethical. What would you gain by just saying to the patient, “Listen, in 20 years you will develop the disease.” It’s unethical. So we are entering into the era, not only of prediction, but we have to think about prevention. This means that we need to have drugs, research, or means by which we can clean, suppress the production of those

deleterious autoantibodies before the damage will accumulate so that the patient will be clinically overt.

In some ways we do have some measurements. But I would like to refer to one of them, which is very simple, it's cheap, and it has no side effects whatsoever. And this is vitamin D. It has been found that vitamin D, given in large amounts—which, by the way, are completely non-toxic—can halt, can reverse, in many situations, definitely in animal models, most probably also in some human beings or in some conditions in human beings, many reduce the production of those deleterious antibodies. So we are talking not only on prediction, but we should refer more to the act and to our ability to prevent the eventual development of autoimmune diseases.

Dr. O'Bryan: Well that is brilliantly said, and that is the foundation of this entire summit, is that all of our listeners understand that identifying a condition or a mechanism is of some value. But it's really, what do you do about that? And in this case, when these antibodies are identified years before there are any symptoms it gives us a window of opportunity to address some of the mechanisms, perhaps in our lifestyle, perhaps in our dietary choices, **[20:00]** which may be contributing to some of the inflammation and some of the development of these antibodies.

Dr. Shoenfeld: Yes. I just wanted very much to compliment your words because I have referred to means and measurements, and you have extended on the issue of lifestyle, and I would like to refer to it. But you are absolutely right. For instance, what we call the healthy diet, low in saturated fatty acid for instance, can change completely the picture, for instance, of systemic lupus. Also, physical activity, avoiding the sun, exposure to the sun, which may be also damaging, especially in subjects who are at risk of prediction, at risk of developing lupus.

In the last ten years the role of smoking was shown to be a detrimental in many diseases by the fact that smoking into the lung changes the structure of proteins in our lung and in our body, which then are not recognized as our own. And therefore it's not anymore a friendly fire, it's a fire against something that has been changed by the smoking. So it started with a disease called Goodpasture syndrome, in which the lungs and the kidneys are affected. And it has been found that those that were affected are mainly those who were smokers.

But in the last several years it has been found to be extremely important in systemic lupus, rheumatoid arthritis, and in other classical autoimmune diseases. What is more clever than to stop something that is not necessary, even though it's unpleasant to suddenly withdraw from smoking? But smoking is a great example of changing behavior—and, as you've mentioned, lifestyle—to avoid not only aggravating a disease

that exists, **[22:30]** but most probably preventing the eventual development in somebody who was found to be at a higher risk to develop the autoimmune condition.

Dr. O'Bryan: Thank you. Very, very well said! Professor, you had referenced a moment ago about high doses of vitamin D that may be able to arrest, and in some cases reverse, the development of autoimmune conditions. What types of dosages have you seen published in the literature that are being used for that?

Dr. Shoenfeld: Yes. The point with the literature and the opinion of vitamin D is that it has been successfully shown to be beneficial in many, many models of autoimmune diseases in animals, from SLE to multiple sclerosis, from Crohn's to diseases which are polymyositis, and so forth. The problem is to show the beneficial effect in patients. You started your words by saying that autoimmune diseases are multi-factorial, and therefore it's quite difficult to show the beneficial effect in a classical way in a disease which is multi-factorial. But despite that, despite the difficulties, there are already papers showing in patients with autoimmune diseases effects on pains, on inflammation, on incidents of attacks, which we call exacerbations, and so forth.

Yet having said that, vitamin D is very cheap, does not need a prescription of a physician, has no side effects whatsoever, and has many additional beneficial effects rather than only on the immune system. For instance in a disease called antiphospholipid syndrome, a classical autoimmune disease which is the cousin of systemic lupus erythematosus, in which the missiles, the autoantibodies, cause fetal loss, or what we call recurrant abortions, as well as **[25:00]** thromboembolic phenomena, recurrent thromboembolic phenomena, which may be represented by recurrent cerebrovascular accidents, emboli to the heart or to the lung or to the peripheral vessels.

We have shown very clearly that the vitamin D can reduce significantly the effect of the missiles on the clotting system. Thus taking the vitamin D may serve as a life-saving drug in those patients in the way that it will prevent cerebrovascular accidents. So I think that vitamin D represents a classical way that we have to think for the future how to avoid eventual development of autoimmune disease. Needless to say that it will depend on our ability precisely to predict who is really at risk, like first-degree relatives of patients who have all the autoimmune disease, because almost all of autoimmune diseases are genetic. Maybe to determine the specific genes or markers with some diseases which are highly associated, for instance, with a marker called HLA. And also analyzing additional blood tests, simple blood tests, which may indicate that the subject, the healthy subject, is at greater risk of developing a specific immune disease.

Dr. O'Bryan: For all of our clinicians who are listening, and the general public, this is one of the points that we have made in our autoimmune seminars when I do a full day

for practitioners. And that is, if there is a history of miscarriages in the family, unexplained miscarriages in the family, then every woman of childbearing age would benefit from having the antibodies checked for antiphospholipid syndrome.

And for our clinicians, that is anti-beta 2-glycoprotein-1 antibody. **[27:30]** If you just check for that, if there's a family history, you check for that. If that woman has elevated levels of that particular antibody, it gives you a window of opportunity to address what may be triggering the production of those antibodies. And as we've already talked about, vitamin D is one of those components, and you would want to check her vitamin D level.

For all of our clinicians and the general public, there is a wonderful website called vitamindcounsel.com. And this is a group of scientists who decided to carry out the technical cutting-edge information to the general public because it wasn't getting out there fast enough. And you will see some of the world's experts on vitamin D writing their papers there. It's a wonderful reference site to learn more about vitamin D.

The point is, if you check for beta-2 glycoprotein-1 antibodies in a healthy woman of childbearing age with a history in the family of unexplained miscarriages, you now are practicing predictive autoimmunity. You're looking for what this patient might be at risk for and seeing if you can nip it in the bud, so to say, if you can identify the lifestyle factors that may be of benefit in reducing that antibody load.

In my practice I have seen that three times where young women of childbearing age had elevated antibodies. I checked them because of a family history. And within one year we were able to bring those antibodies down to normal range three times. And it was by changing lifestyle, changing diet, and addressing nutrition.

Dr. Shoenfeld: Just to complement your wonderful explanation, I saw today a 60-year-old lady, a beautiful lady, who went through 3 events of what we call TIA, transient ischemic attack. Luckily enough, the attacks didn't leave any damage, any paralysis, or hemiparesis or hemiplegia in her body. Her story was remarkable by the fact that her daughter, who is now 40 years old, had also an event of CVA in the past. And the daughter was found to suffer **[30:00]** from a genetic marker of blood coagulation or hypercoagulation, MTHFR.

Now, when she was admitted to the hospital, they were looking also for this blood coagulation defect. Only, after the third TIA, high levels of anti-coagulating as well as anti-beta 2-GPI, as you mentioned, were found to be very high. Needless to say that this patient will have to stay on anticoagulation for life. But the more interesting lesson from that is that her daughter—and by the way, her son, who is asymptomatic—too, should be checked for the autoantibodies. Needless to say, if the daughter will be found

to have these autoantibodies, she also would have to be on anticoagulation, Coumadin, for life.

The other question is, what about the son? There is a paper now in *Blood* indicating that there are some patients who might be even in a higher risk of hypercoagulation, even though they are completely asymptomatic. If they do have what we call antibody-triad positive, namely high levels of antibodies against anticoagulating, high levels against anti-beta 2-GPI, as well as a third autoantibody, which is extremely important, lupus anticoagulant. And, the authors, headed by Victoria Pengo from Italy raise the suggestion that these asymptomatic completely healthy subjects carrying the triple positive autoantibodies, if especially they have additional risk, let's suppose MTHFR, or if they are, for instance, obese or smokers or having hypertension, these are the patients that should be preventably treated with full anticoagulation. **[32:30]**

This is still in dispute. There is a difference between full anticoagulation and vitamin D. Vitamin D has no side effects, whatsoever. And, therefore, if I can a little bit disagree with one small comment that you said, namely measure vitamin D, I wouldn't measure vitamin D. I would have given it without any hesitation even if the levels are normal. The higher the better. But with anticoagulation, in contrast to vitamin D, there is some risk. So currently there is no final consensus yet, whether we should fully anticoagulate.

And what I do, I present the dilemma and the options to the patients. I do also check, who is the patient? Is he intelligent? Can I rely on the ability of this patient to measure his coagulation state, namely the INR level. And then I will tell the patient, "It's your decision whether you should take the full anticoagulation or not." If we all have final consensus that, indeed, it's preventive, then we physicians, the general practitioners, and more professionals, we should prescribe it definitely and try to convince the patients that the benefit of taking the full anticoagulation is much higher in comparison to the risk of having, for instance, bleeding due to the anticoagulation.

Dr. O'Bryan: I'm smiling as I'm hearing you lay out your thought process, professor, because I would look forward to sharing a glass of wine with you at some point, and doing a little battle with you because—

Dr. Shoenfeld: I would love to drink a glass of wine! Coming from Israel, I wouldn't love to have a battle. But I invite you to join us in the Ninth International Congress of Autoimmunity, which will take place in March in the beautiful city Nice **[35:00]** in the French Riviera. And you can join the 2,500 people. But the glass of wine will be on me!

Dr. O'Bryan: Thank you for that invitation! Thank you. I'm going to refer to a case study that I often reference in my seminars for doctors. This comes from the *World Journal of*

Gastroenterology in 2003. And it was La Villa, I believe, who talked about a 34-year-old woman who presented to the hospital after having a second unexplained miscarriage. And they found a number of functional problems, such as increased pancreatic enzymes and increased liver enzymes, but nothing that really explained the loss of the pregnancy until they checked her for antiphospholipid syndrome.

She had antiphospholipid syndrome. She had elevation of those antibodies that we referred to, beta-2 glycoprotein-1 and cardiolipin. And she also was anemic. So, they checked her and found out this patient was a celiac. They put this patient on a gluten-free diet with no other treatment protocols whatsoever. And within twelve months, all of the beta-2 glycoprotein-1 antibodies, the cardiolipin antibodies—she also had thyroid antibodies that were elevated—they all came back down to normal range. This appeared to be that there was an environmental trigger—in this case gluten—for this individual, which is the premise of this entire summit, is that in some cases, and it's many, gluten is an environmental trigger. In this case, it was an environmental trigger that appeared to be fueling the autoimmune mechanism producing these missiles.

So, as a clinician with the case that you just presented, professor, of the woman who presented with her third TIA—and for our listening audience, that's almost like a mini stroke, it looks that way, but this woman did not have any damage which was excellent—I would suggest that as a clinician I would be monitoring her INR levels to make sure that her clotting processes **[37:30]** were not at risk. If they were, I would have her on the medications, absolutely. But I would be monitoring that as her autoimmune antibodies come down, did her risk of clotting also come down?

And if that risk of clotting comes down, I would recommend to her, "Keep working with your physician to monitor you. And as the risk goes lower, see how that physician feels about lowering the doses of the medication that you're taking. Do you need as much?" So you always work with the physician who recommended the medication, but have some markers that you can use to determine if you continue to require these same dosages or the need for the medication at all.

And given that we have so many clinicians listening to this, professor, would you find some vulnerabilities in that line of logic that you would wish to comment on?

Dr. Shoenfeld: Yes, you have raised many issues, so I will try to be short. I would like first of all to refer to the prediction of pregnancy loss. I believe that we had a paper which listed many markers that may predict fetal loss. And among them are those that you mentioned. First of all, the antiphospholipid antibodies, which we call APLAs, the three. There are additional, by the way, to these three. Actually, we have a paper referring to four key different autoantibodies in the antiphospholipid syndrome.

There are what you mentioned, the anti-thyroid antibodies--anti-thyroglobulin, and anti-TPO--which in another paper we have shown that the anti-thyroglobulin antibodies being injected into mice will cause per se fetal loss, although there is a great association between autoantibodies against thyroid constituents and fetal loss or abortions. And, last but not least, the celiac antibodies, per se, the anti-transglutaminase and anti-endomysium, they all will cause a pregnancy loss.

But the second point that you have mentioned is the interaction or the effect of the environmental factor, **[40:00]** in this case gluten, as the initiator of the production of the other autoantibodies like the beta2. It's quite, I would say, conceivable that gluten might be like that. Actually, if you take many autoimmune diseases and you measure for other autoantibodies, the nonspecific autoantibodies, needless to say that the anti-gluten antibodies, the antigliadin, will pop up as the most prevalent with other autoimmune disease.

And here I would like to refer to the disease multiple sclerosis. Multiple sclerosis, when we have measured other autoantibodies, in eight percent, eight subjects, eight patients out of one hundred, we found anti-gluten antibodies. And at first we tended to neglect it as a nonspecific, as an epiphenomenon until we went to the literature and we found that there was a very famous neurologist who had multiple sclerosis, found in his blood the anti-gluten antibodies. And he refrained from gluten or actually used a gluten-free diet. And he entered into a complete long remission from the multiple sclerosis indicating, not only what you referred to, that the gluten may induce the autoantibodies, but it may induce the disease or be responsible for the disease.

However, when people were very happy to follow the case report that he published on himself, they found that in most of the cases the gluten-free diet was not effective in multiple sclerosis. We believe that we have the explanation for that. Mainly, it's only in those that you find the anti-gluten, in those you will take the gluten-free diet. And, unfortunately it's only eight percent of those patients with multiple sclerosis.

So the lesson to take home is, first of all, to measure the whole panel of autoantibodies, including anti-gluten—gliadin—anti-thyroglobulin. **[42:30]** There are already chips which may measure 20 or 30 different autoantibodies. And, like Martin Luther King has said, my dream is that we will have very soon a chip of over 500 different autoantibodies, which in the same chip will measure also the genetic markers of the patient.

So we will, as a physician using the proper programs to analyze so many data, we will be able to recommend that patients work with you in the future from the point of view of prediction, but moreover, the prevention.

Dr. O'Bryan: Very well said, thank you, very well said. In the journal *Diabetes*, there was an article published by Vaarala entitled the "The "Perfect Storm" for Type I Diabetes: A Complex Interplay Between Intestinal Microbiota, Gut Permeability and Mucosal Immunity." And the paper went on to talk about how each of those components can play a role in the development of that particular autoimmune disease, type I diabetes.

One of our guests on the summit was Dr. Alessio Fasano, the Chair of Pediatric Gastroenterology at Mass General at Harvard. Dr. Fasano tells us the trilogy in the development of autoimmune mechanisms includes a genetic vulnerability, an environmental trigger—which I refer to as "the straw that broke the camel's back"—, and intestinal permeability.

What have you seen in your research in terms of that overview? Does that appear to be an accurate overview of intestinal permeability, gut microbiota, genetics, and environmental triggers as being very strong contributors, and almost prerequisites, in the development of autoimmune conditions?

Dr. Shoenfeld: I know very well Outi Vaarala. And I don't know very well my dear friend Fasano, who is a great physician and a great lecturer. And I do agree with the observation which **[45:00]** we have described in the past, and the book that you have referred to has a long introduction which you introduced me, *The Mosiac of Autoimmunity*, mainly that all autoimmune diseases are multi-factorial. And even if we don't see some of the factors, they do exist. We have to look for them. There's no question that there is genetic, really the genetic. The genetic actually determines how foreign substances or maybe our own substances, autoantigens in our body, will be presented to the immune system. For instance, HLA-DRB1 and all its group of HLA, they are notorious. And it seems like they are presenting the autoantigen in a stronger way to the immune system in comparison to those who do not carry HLA. Therefore they are so prevalent in my patients with different autoimmune diseases.

The second point is the environmental factor. And among the environmental factors there are bacteria and physicians. Bacteria because they mimic many of our autoantigens and raise fire against themselves. And then it's redirected to our own body, which we call molecular mimicry. But there are additional mechanisms. Physicians because we prescribe drugs, and there are many reactions against the drugs which also confuse the immune system.

Now when we talk about drugs, one of our organs which is the most, I would say, full with bacteria is the intestine. So the microbiota is most probably one of the most important environmental factors—even though it's inside in our body, but let's call it an environmental factor—which must not only determine many autoimmune disease, but

determine other diseases too. Whether it is the **[47:30]** effect on the permeability or it's the effect just by presence and changing different things in the intestine, it's still is a debate.

But there's no question that if we talk about preventive measurements that you related so much to previously, so adding probiotics to our armamentarium of prevention of autoimmune disease would definitely help in reducing the risk in those subjects which are at a higher risk of developing autoimmune diseases.

So whether the final mechanism is permeability, whether the final mechanism is just molecular mimicry like we have, for instance between helicobacter jejuni and neuronal substances, which is responsible for glandular syndrome, with or without increased permeability, it would be changed if we would change the environment in our intestine by probiotics.

Let me just finish this explanation. But one disease which is very remarkable is called idiopathic thrombocytopenic purpura. It's ITP. It's called idiopathic because in the past we physicians were idiots that we didn't know the pathology, idiopathic. And therefore today it has been changed to immune thrombocytopenic purpura. This is a classical humoral-mediated autoimmune disease in which the child, sometimes the adult, develops autoantibodies against constituents of the platelets. And, then the couple, the platelets with the autoantibodies are consumed in particular in the reticuloendothelial system, in the spleen and sometimes also in the liver.

It's also been found that this disease is associated very closely with a helicobacter pylori. And the cross-reaction in the antigen between the bacteria and the platelets was delineated. **[50:00]** And this is one of the diseases. There are some other examples in which eradication of the bacteria by antibiotics—the three antibiotics—will cure the autoimmune disease.

We don't have many autoimmune diseases which we can cure with antibiotics because when we diagnose the patients, all of the horses run out from the stables and therefore the disease perpetuates itself. But in the case of the child with the helicobacter pylori, giving the antibiotics is really a nice example of how the intestine, or in this case the gastric bacteria, induces the disease, eradicating the bacteria, cures the disease.

Dr. O'Bryan: That is a very eloquent, groundbreaking concept that I'm going to summarize for our general audience. Many of us have heard of H. pylori, helicobacter pylori, as a bacteria contributing to the development of ulcers. And what the science is now showing is that the H. pylori, when the body makes antibodies to H. pylori, that it may cause the term is "molecular mimicry", and the body starts making antibodies to its own clotting mechanisms. And one can develop this disease called ideopathic

thrombocytopenic purpura. By getting rid of the bacteria in the digestive tract, the helicobacter, we reduce this autoimmune disease that is such a terrible disease to have.

This is a classic example of where an antibiotic dealing with the gut bacteria may have a direct effect on the development of an autoimmune condition. So for our clinicians we have another tool in our chest when we identify H. pylori in our patients maybe because of GI upset and we look for H. pylori. If we find H. pylori it may be of value to be looking for the antibodies to ideopatchic thrombocytopenic purpura also, to see if the patient is at risk there.

Dr. Shoenfeld, one last topic I would like **[52:30]** to bring up with you please. It's commonly thought that the number one cause of morbidity and mortality in the industrialized world is cardiovascular disease. That's been accepted for many, many years. But you have put out a five-page list of research studies looking at the autoimmune contribution to cardiovascular disease, that there is a strong immune component.

Can you tell us what role you feel the immune system has in the development of cardiovascular disease?

Dr. Shoenfeld: Yes. When you listed the books that we have written and edited, you didn't list one book which was called *Atherosclerosis and Autoimmunity*. We started many years—we were not the first ones—to allude to the idea that also atherosclerosis, in addition to being caused by the classical Framingham risk factors like hypertension, diabetes, lack of exercise and so forth, is also caused by autoimmune factors like the autoantibodies.

One of the classical autoantibodies that are found in the blood of those patients is anti-oxidized LDL. By the way, we have different anti-oxidized LDLs. Some of them are pathogenic causing that atherosclerosis. Some of them are protective. Interesting. And it has been found that in most of the autoimmune diseases, a systemic one like lupus, rheumatoid arthritis, and others, you have what we call accelerated atherosclerosis. Actually, the patients, especially the young patients, they die fifty times more from acute myocardial infarction than their age range controls.

So there are different components which accelerate the cardiovascular diseases. One of them is the presence of the autoantibodies. But the other is the inflammation **[55:00]** per se, which, for physicians, can be represented in the blood with a notorious molecule called CRP, which denotes C-reactive protein. Actually, it was supposed to be a protective protein against bacterias. But it seems that this protein was supposed to be protective. And there's no free lunch. It's actually pathogenic for atherosclerosis. It is deposited in the blood vessels and induces a cascade of accelerated atherosclerosis.

So accelerated atherosclerosis, cardiovascular disease, cardiovascular morbidity and mortalities in autoimmunity have autoantibodies per se, being an autoimmune disease per se. And in addition, because of the other systemic autoimmune diseases, the generalized inflammation adds to this accelerated process of atherosclerosis. And definitely, physicians as well as general practitioners specifically, should pay attention to reduce any risk factors, the generalized ones, hypertension, obesity, diabetes and so forth, as well as the most specific, the autoimmune one in those patients who are at risk, mainly the patients with autoimmune diseases.

Dr. O'Bryan: Thank you very much for that. Well, Dr. Shoenfeld it has been an extreme honor to spend this time with you. And you have given us so many pearls to ponder and to include in an overview of the mechanisms of how an environmental trigger such as gluten may contribute to diseases outside of the gut.

And as one of your references earlier was to Martin Luther King and that his very famous phrase, "I have a dream," you, sir, are a prophet leading the way for us to understand this world of predictive autoimmunity **[57:30]** and the value that it brings in working with our clients and with our patients to identify these mechanisms years before there's so much damage that the tissue is now giving us symptoms. And if we can identify it, we then have an opportunity to address it, to do something about it, to try to turn around the direction we're going in.

Thank you very much for taking the time to be with us today!

Dr. Shoenfeld: It's my pleasure. Thank you!

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