WOMEN AT THE PAS

To Find a Means To Keep Looking

Prof. Anetta Undas from the Jagiellonian University Medical College discusses the sinister force of diseases, the commandments of scientific editing, and the patriotism of scientists.

ACADEMIA: **You have established a center for fibrin research. Fibrin is a protein that is generated from fibrinogen during the clotting of blood and represents the key component of blood clots. To what extent could your research help understand the causes of the dangerous manifestations of coagulation disorders and optimize their treatment?**

ANETTA UNDAS: Most of what I have accomplished as a scientist is related to the pathophysiology of the thromboembolic complications of cardiovascular diseases as the most prevalent diseases and the most common causes of death in developed countries. In particular, this pertains to myocardial infarction, brain stroke, pulmonary embolism, and venous thrombosis in different parts of the body, which affects around 1-3 persons in every 1,000 adults. My work is a good example of interdisciplinary research, at the intersection of clinical studies and basic science. Over the past 10 years, my interests have focused on fibrin, or the final product of the coagulation process that is formed from fibrinogen in a thrombin-catalyzed reaction. I study the factors that determine why the structure of the fibrin meshwork and consequently its mechanical properties and activity, especially its susceptibility to enzymatic degradation, vary so greatly among humans. In one person, blood clots will contain densely packed and thin fibers of fibrin that form networks poorly permeable for fibrinolytic proteins and hard to dissolve in order to maintain or quickly restore blood flow in the vessel. Another person will show a tendency for the formation of the fibrin mesh with relatively few strands that resemble tangled threads and are susceptible to the action of strong endogenous and externally administered lytic enzymes. Sometimes fibrin has a highly irregular structure with clusters of densely packed strands – between these strands, the mesh becomes loose and susceptible to dissolution. The processes that determine this heterogeneity are partly genetic and partly affected by transient factors. For example, inflammation or cigarette smoking render the fibrin mesh dense and resistant to lysis. As we already know, this means an increased risk of myocardial infarction, ischemic stroke, and recurrent venous thromboembolism. In addition, my recent work published in *Stroke* shows that such a dense structure reduces the effectiveness of anticoagulant therapy, at least in patients with atrial fibrillation. The disease leads to the brain strokes associated with the worst outcomes, with a risk of death of even 25% within 30 days from the onset. We still do not know the mechanisms that regulate the structure of the fibrin mesh, many things have yet to be discovered. Specific fibrin-modifying drugs are currently under investigation, and there are high hopes for such medications.

You are the lead author of papers that were published in *Blood*, in *Circulation* and in *Arteriosclerosis, Thrombosis, and Vascular Biology*, presenting the impact of cholesterol-lowering drugs on blood clotting. Can this mechanism of action prevent heart attacks, brain strokes, and venous thrombosis?

There's no doubt that my greatest achievement, especially judging by the number of citations, has been the discovery that the administration of powerful cholesterol-lowering medications called statins – the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors – has numerous effects at several stages that lead to the production of thrombin and the formation of fibrin, which is the most important component of most blood clots in vessels in terms of volume. It only takes three doses of such medicines, routinely prescribed to patients with a stable atherosclerotic vascular disease, to observe a 20–30% decrease in the speed of reactions conducive to the generation of thrombin, the key coagulation enzyme, and, at the same time, the impairment of anticoagulation mechanisms, chiefly through the protein C system, which is best visible where it should be visible, namely at local sites of vessel wall injury. That is a natural stimulant that activates hemostasis. The "anticoagulation" action of statins is not associated with the magnitude of cholesterol reduction. It is poorly correlated with this crucial property of statins. For over 15 years, the proposals were put forward that statins should be a good therapeutic option not only in myocardial infarction and brain stroke, where the clinical efficacy of such medications correlates well with a reduction in cholesterol concentrations, but also in the prevention of the first and recurrent episodes of venous thrombosis and/or pulmonary embolism. For several years, however, the data corroborating that hypothesis were far from convincing. The findings of the JUPITER trial, announced in 2009, provided strong support for those who advocated the concept of the clinically significant effects of statins, showing an around 20% reduction in the risk of venous thrombosis after two years of treatment with one of such drugs, rosuvastatin. That resulted in renewed interest in my papers on statins from back in 2001–2005 and increased numbers of citations. In science, patience pays off.

You have devoted several papers to changes in the coagulation system in such autoimmune diseases as rheumatoid arthritis, whose prevalence in the general population is growing. Could such changes be of any clinical significance?

Most of the autoimmune diseases, in particular rheumatic diseases, including not only rheumatoid arthritis but also systemic lupus erythematosus and systemic sclerosis, are associated with an increased

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risk for thromboembolic events, especially arterial episodes. The mechanisms, as the literature usually says, are either unclear or poorly studied. My small contribution to the field has involved demonstrating that in patients with rheumatoid arthritis, inflammation increases the synthesis and activity of coagulation factors, especially factor VIII, increasing thrombin generation in the circulating blood, which is conducive to thrombosis. In the context of rheumatoid arthritis, we were also the first to describe the abnormal, dense networks of fibrin that are not easily dissolved even despite the presence of substantial levels of fibrinolytic enzymes. Today, we know that the suppression of inflammation in such diseases is the only thing that can improve the hemostatic balance, thus reducing the risk of thromboembolic events. Such data provide additional arguments in favor of strong and dangerous relationships between inflammation and blood coagulation, not only in rheumatic diseases.

What National Science Center project are you currently working on?

The grant I've received is aimed at explaining the mechanism behind the prothrombotic properties of the fibrin mesh in patients with acute arterial thromboembolism. It is a common disease that kills around 10% of patients within 30 days, and this share is even larger among the elderly. One example was the healthy and fit champion hammer thrower Kamila Skolimowska, who died of pulmonary embolism at the age of 27. That illustrates well the sinister force of this disease, which is often very insidious. Nonetheless, it is worth stressing that pulmonary embolism, just like venous thrombosis, can be prevented and treated successfully in most cases. Nonetheless, pulmonary embolism continues to hide many secrets. Most of the material that occludes pulmonary arteries of various sizes consists of fibrin, which winds around red blood cells. For that reason, characterizing the structure and activity of the fibrin mesh in this disease and their changes in the course of anticoagulant therapy in the first hours after diagnosis may help identify patients with a satisfactory response to standard therapy and those who may need other treatment. It remains unclear if long-term prognosis and subsequent complications may depend on the properties of fibrin clots at the onset of acute pulmonary embolism and after 24 hours of treatment with various anticoagulation drugs. I'd like to explain this in my project. I'm aware, though, that to find an answer means to keep looking and asking questions. That's what I like most about science – the endless unknowns and question marks, whose number grows with every question we've answered.

You are the editor-in-chief of the monthly *Polish Archives of Internal Medicine (Polskie Archiwum Medycyny Wewnętrznej)*. What is your opinion about the caliber of Polish scientific journals, compared with top journals as well as similar periodicals in the neighboring countries?

I'm proud of *Pol Arch Intern Med*, the official journal of the Polish Society of Internal Medicine. It has been published since 1923, and I've been its editor-in-chief since 2008. Since the beginning of 2017, the monthly has been published as *Polish Archives of Internal Medicine*. The journal has achieved considerable success, given the position of Polish science and Polish universities in the world, as demonstrated by its impact factor (IF) for 2016, which was 2.309. That gives us a leading position among Polish and Central European clinical journals. For six years, I was a member of the ministerial commission for science promotion, responsible for funding for scientific journals, and I was absolutely astonished to see that hundreds of journals received public support every year. A vast majority of them, despite existing for more than a decade, sometimes several decades, were still essentially "operating undercover" – they were known only to a small group of supporters and had no idea how to reach out to a broader group of readers. The number of Polish journals with impact factors is growing, but it's in a slow increase, and their impact factors are definitely higher and higher at an even slower rate. They have difficulty reaching the relatively high value of IF=2. There are plenty of reasons behind this situation, but my journal shows that blaming underfunding and the low level of Polish science for this is an oversimplification and a poor excuse. My diagnosis is as follows: efforts to build the position of scientific journals and institutes are always based on one fundamental rule that is actually very simple, namely the rule of scientific excellence. It should be the first and only commandment of scientific editing. Consequently, a paper should be above all evaluated objectively by the editor. Only a paper that includes new and important observations should be reviewed by external experts and sent back to the author for improvements, or with reviews that justify its rejection within 28 days on average. Irrespective of which authors and which institutions the articles come from, no exception. This must be coupled with a considerable amount of passion and a sense of mission, involvement in something important, worth the effort. In August 2017, Dr. Joseph A. Hill, editor-in-chief of the weekly *Circulation*, regarded as the world's best cardiology journal, wrote in editor's page that he had been even called a "mass murderer" by embittered authors whose papers were not received enthusiastically by reviewers, because as they saw it he had deprived them of the chance to address important clinical questions. I've not been told that yet, but threats and complaints are daily occurrences, and we must be prepared for that. When building and continuing to strengthen the position of a journal, we in a sense influence the scholarly community, the future and past authors, by suggesting how they should improve their papers, accept criticism, and treat comments as valuable guidelines for the future. I deeply believe that many journals can improve their position as a result of the change in the Polish Ministry of Science and Higher Education's policy of supporting journals, which is now focused on the quality of support for the best, those who can join at least the second league of scientific journals in their respective fields, and efforts to stop wasting money on the journals that are not good enough and have shown no ambition for years to join the group of recognized international journals.

What character traits should a scientist have to succeed in his or her field?

With each year, I have the growing conviction that it's impossible to achieve success in science without perseverance. That's the most important thing. It is largely inborn, you can't learn it. It is perseverance that prevents you from becoming discouraged when your findings are inconclusive, your research papers get negative reviews, your grant applications are rejected, there are staff shortages, and the almost ubiquitous red tape extends the length of most of the research activities beyond what is initially hardly imaginable. Perseverance is usually coupled with something extremely useful, namely resistance to failures and what is often malicious or even insulting criticism. Resistance shown by researchers should be equal to that of consummate politicians. The caravan goes on, because the purpose, the idea we believe in gives us the strength that keeps us going. A researcher's passion and endless curiosity never fail. Real researchers know that everything they plan, describe, present in their projects and papers is not perfect, but their perseverance and constant, insatiable passion to explore the unknown make them fight for their ideas. Such ideas can be modified with the necessary amount of humility in the face of constructive criticism, but perseverance will protect the core of the concept, the creative contribution, the opinion in scientific discussions that we want to share with other researchers. Being a researcher means the joy of putting forward hypotheses, the joy of noticing non-obvious links, possibilities that have so far eluded other smart colleagues, the joy of the adventure in which scientists, like the famous 19th-century travelers, define the direction of the journey and the ways of reaching their destination, and have the right to change the route when another destination proves more intriguing and worth the effort. In my opinion, science is also something for restless souls and doubting Thomases, who are prepared to spend a lot of time and put a lot of effort into checking why something happens and if that can be changed. The job of a scientist is essentially fun – it means anticipating the results, feeling joy about a successful experiment, and feeling disappointment, which will be soon alleviated by passion. It will prompt another idea, and it may be even better than the previous one, which come to think of it was not so brilliant, and so on, until the next result. Constant challenges and tasks – that's the essence of science.

In Poland, spending on science has been very low for years, still below 1% of the GDP, which gives us a place at the tail end of Europe. How can we make important discoveries in such conditions?

Despite a substantial improvement in this field, as demonstrated by the funding for National Science Center grants over the past three years, Poland spends less on science as a country than for example the budget of Stanford University, which ranks second in the Shanghai ranking of universities. So working as a scientist in Poland is somewhat heroic. However, perseverance and passion can achieve a lot. Modest funding teaches us to manage our money well and invest in young people, because the future of Polish science belongs to them. Support that is provided by experience gathered during foreign trips, research fellowships, and often long-term collaboration with foreign researchers is fundamentally important. Being a scientist is therefore essentially prestigious, and universities and institutions responsible for central funding should notice this and provide institutional support, recognizing the best and appreciate them. Justice in science means exactly the survival of the best, the development of the best, those who are open to new ideas, technologies, contacts with people who are better than them in an environment that appreciates them and consists of the best centers. I am often asked, in one form or another, why I try so hard, if working as a medical doctor, which is often supported by income from commercial clinical trials, would give me a lot more money than the salary of a university professor and research grants. How can we explain something that eludes the rational, generally understood motives that guide most employees? How can we explain the curiosity thanks to which we never stop being scholars? And one more thing, I like to repeat after Prof. Marek Naruszewicz, a prominent scientist in the field of pharmacy, that "the work of a scientist in Poland is patriotic in its nature." Polish affiliations in papers appearing in high impact journals, especially if the research that is documented by the paper originated and was conducted at a Polish center, makes Poland visibly present in science. That's our small contribution to the Polish cause.

Interview by **Anna Kilian**
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