ACADEMIA

Fortunate Coincidences

The experimental pharmacologist **Prof. Stanisław Jerzy Czuczwar**, Vice President of the Polish Academy of Sciences, tells us about how he got into medical research, about the search for new epilepsy treatments, and how pharmaceuticals are in a way akin to cell phone towers.

ACADEMIA: **Why did you choose medicine as a career path?**

STANISŁAW JERZY CZUCZWAR: We could say that choosing medical school was a family tradition, because both my mother and my father were doctors. Both graduated from the Medical Academy in Lublin in the 1950s, but neither became practicing physicians: my mother worked as a forensics expert, whereas my father was an anatomical pathologist. I myself am an experimental pharmacologist, which means I do not take patients, but rather work on improving the current methods for treating epilepsy.

After finishing medical school, I did want to devote myself to clinical practice, to become an internist, but the doctoral program only had openings in theoretical fields like pharmacology. And so in a certain sense it was chance that brought me to be where I am.

My two sons are continuing this family tradition, both of them are doctors, but unlike me they are clinical doctors. One is an anesthesiologist, with his mind set on that specialization when he started medical school. The other is a gynecologist, and also already chose that while in medical school.

What does your research involve?

My work is based on animal models. I try to find new drugs exhibiting antiepileptic mechanisms, but at the same time I also work on improving existing therapies, particularly in terms of drug-resistant epilepsy. The disease needs to be treated with at least two different medicines, and I try to find combinations of existing pharmaceuticals that yield the best clinical results.

Experimental practice on animals is increasingly becoming a point of debate. Some people would even like to completely prohibit such experimentation.

We would not have the increasingly better, modern treatment methods now used in medicine without experimental animal models. I realized that some such models are burdensome for the animals, but the dilemma we face is this: Should we halt experimentation and put the brakes on progress in medical practice, or should we continue?

It seems to me that everyone expects new therapies to be developed, including those who are against animal experimentation. Unfortunately, we do not have a good replacement, because the in vitro models or computer models that are postulated cannot take the place of a complex, living organism.

How does one study epilepsy in an animal model?

There are various models of experimental epilepsy. Naturally, one has to evoke convulsive activity, for

PROF. STANISŁAW JERZY CZUCZWAR

instance by applying certain substances. This is definitely burdensome for the animals, but at least the seizures do not hurt. All the currently available antiepileptic drugs, with the exception of the rarely applied phenobarbital, were discovered thanks to such experiments. Modern medications give around 70% of patients full relief from epileptic seizures, whereas just 100 years ago epilepsy sufferers essentially could not be helped at all.

How does the mechanism of epilepsy work?

Most epileptic seizures result from insufficient inhibitory mechanisms in the central nervous system, or from a prevalence of stimulatory neurotransmitters. Both mechanisms may also be at work. The main inhibitory neurotransmitter in the brain is gamma aminobutyric acid, or GABA, whereas the main stimulatory neurotransmitters are glutamate and aspartate. Attacks occur when there is too much of the stimulatory substances, or too little of the inhibitory ones. Apart from that, patients may experience "absence seizures," which involve a loss of consciousness but no convulsions. These attacks probably involve enhanced inhibitory processes, in other words the mechanism is here the opposite of that involved in the other types.

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So what is the etiology, in that case? Are congenital factors decisive, or can epilepsy be acquired?

Epilepsy can be caused by genetic factors, for instance by a certain mutation leading to the malfunctioning of sodium channels in the central nervous system. But convulsions can also be provoked by taking various psychostimulatory substances, especially in large doses. For example, the stimulatory substances of unknown composition that go into "designer" drugs. The problem here is our inability to counteract them effectively, because when we outlaw a particular substance the manufacturers can just modify it slightly and the resulting substance, still toxic, can be sold legally, not figuring on the list of prohibited substances.

The problem in treating such cases of toxic overdosing and the convulsive attacks they provoke is that doctors usually do not know what chemical substance the patient took. Such an individual can essentially only be treated for their symptoms, and sometimes such treatment is not enough. Epileptic attacks can also accompany disorders of the central nervous system, and these are called "symptomatic" seizures. If the cause of a seizure is not known, it is described as "idiopathic."

On the other hand, certain substances obtained from cannabis are used in epilepsy treatment.

Yes, cannabinoids are agonists, in other words they stimulate cannabinoid receptors. There are two types of such receptors, known as CB1 and CB2. Central activity mainly involves receptors of the former type.

My team and I have gotten involved in the study of substances stimulating CB1 receptors and "non-specific" agonists, which stimulate both types of receptors. They turn out to show anticonvulsive properties in animal models, and also to augment the effect of many antiepileptic drugs. The most promising chemical in this group is cannabidiol. It does not interact with CB1 receptors, and so it does not have psychostimulatory or euphoric effects like marihuana does, but it seems to be effective at inhibiting convulsive activity, even though the mechanism of its action has not yet been fully understood. However, fears that it is a narcotic are unjustified, because it does not provoke euphoria or other states characteristic of marihuana. Clinical research is underway using cannabidiol around the world and it may soon become approved as an antiepileptic pharmaceutical. Pediatric patients show a particularly good improvement when using cannabidiol, but for the time being the sample is too small to draw any clear-cut conclusions.

Are substances isolated from cannabis being used in treating Parkinson's as well?

They are being tested with various illnesses. One example being Parkinson's, but also multiple sclerosis and Alzheimer's, where cannabidiol has a positive effect, but this is for now in the preliminary stages of research.

We should point out that there are many varieties of cannabis. The ones that have a narcotic effect are rich in THC, or tetrahydrocannabinol, which has therapeutic applications in cancer patients because it acts as a pain killer and mood booster. But varieties rich in cannabidiol and low in THC content

can be used in treating epileptic seizures. THC can be made synthetically, but preparations obtained from cannabis plants are typically used in such therapy.

It appears that the very same substance itself can be used as a drug or as a poison, depending on the dose.

To tell the truth, every drug is essentially a poison, beneficial in therapeutic doses but toxic at higher concentrations. When a dose is too high, negative symptoms are visible in everyone. But side effects, such as dizziness, can occur in some patients even at smaller doses. However, it should be borne in mind that sometimes there is a different mechanism at work here. If the informational pamphlet lists possible side effects of a drug, then certain individuals may experience them.

Like a placebo effect, only working negatively?

Yes. A drug that does not have any side effects generally does not have any clinical action, unlike in the case of the placebo effect. The placebo effect is evident, for instance, in clinical studies on large groups of patients, and it is sometimes so strong it is even hard to demonstrate the effectiveness of the substance being tested.

But the power of suggestion also operates in other fields. Perhaps I'm getting a bit off-topic here, but it's an interesting issue. Many people feel that cell phone towers are harmful and cause sleep disorders, dizziness, headaches, and malaise. And although towers are erected beyond the regulation distances from homes, a group of residents usually comes forward to demand that they should be removed. To study whether the reported effects were real, dummy towers were erected. Some people living near them began to complain about the characteristic maladies, even though the towers were not actually operating.

That illustrates how huge non-pharmacological effects can be when drugs are tested. We may observe a placebo effect both in the positive sense, when a neutral substance causes an improvement, and in the negative sense, when a substance causes unwarranted side-effects.

You have also studied the use of antiepileptic drugs as neuroprotective substances, those that protect nerve cells from damage in acute conditions of brain damage.

Yes. Even a single epileptic seizure causes the death of some of the neurons in the brain, as has been confirmed in research with animals and through post-mortem analysis of the brains of epilepsy sufferers who experienced many attacks. Large areas of their brains underwent neurodegeneration, most likely as a consequence of those seizures. Neurodegeneration is also related to the process of epileptogenesis, by which a properly functioning brain turns into one generating epileptic seizures.

It was suspected that neurodegeneration causes more profound epileptogenesis and increased convulsive activity. Intensive research discovered that certain antiepileptic drugs, like valproate or the newer levetiracetam, do indeed protect nerve cells from degeneration, yet others do not, such as phenytoin or carbamazepine. Interestingly, neuroprotection does not always go hand-in-hand with impeding epileptogenesis. It is currently thought that the process of epileptogenesis is significantly more complex, with neurodegeneration being one of the factors affecting the dynamics and scope of the process.

For a single drug to be created, around 10,000 different substances need to be synthesized and many of their modifications tested, with different functional groups. **Sometimes pure chance can help**.

Do antiepileptic drugs have applications for other illnesses?

Yes, attempts are being made to test them in Alzheimer's; for instance levetiracetam is being so studied. Some of the antiepileptic drugs have antidepressant properties and can be used supplementarily in patients with depression, alongside typical antidepressant drugs. On the other hand, epilepsy patients frequently suffer from depression. Because it is suspected that some of the antidepressant drugs may provoke epileptic seizures, doctors always face the dilemma of how intensive therapy should be. This conundrum can be aided by an antiepileptic drug that simultaneously has antidepressant properties. Of course, there are many effective antidepressant drugs that do not negatively contribute to convulsive activity.

Where do new drugs come from? There are millions of molecules with potential biological action, how can you find the right one?

For a drug to be created from a given chemical group, around 10,000 different substances need

to be synthesized and many of their modifications tested, with different functional groups. Sometimes pure chance can help. The therapeutic properties of valproic acid were discovered by one such fortunate accident.

Valproic acid was used as a solvent for many organic substances in water. In the 1960s, researchers from the French company Synthelabo were testing derivatives of a number of potential anticonvulsive substances. They all turned out to work very well, so they began to test lower doses. In pharmaceutical research, one seeks to identify the smallest dose of a substance that still evokes the desired effect. So, first one tests, say, a dose of 100 mg/kg of body weight, then 10 mg/kg, and so on. In this case, the researchers went down to what might be called "homeopathic" doses, yet still observed anticonvulsive action. This was completely incredible, and they eventually realized that the anticonvulsive substance was actually the valproic acid, not the molecules being tested in tiny doses. This marked the discovery of one of the most effective antiepileptic drugs, which is still used today with very good therapeutic effect.

In that case, the right substance was unwittingly used as a solvent. How about in studies carried out in a more systematic way?

There are many methods. Modifications of existing drugs are tested, trying to find derivatives with a significantly better pharmacokinetic profile (e.g. absorbed better by the digestive system), fewer side effects, and stronger anticonvulsive action.

In the 1980s, I was a stipend of the European Science Fund at Prof. Meldrum's lab at the University of London. During that time, work was starting on antagonists of glutamic acid and I was one of the first to study the action of NMDA receptor antagonists, belonging to a subgroup of glutamic acid receptors. After returning to Poland I still had access to the

Prof. Stanisław Jerzy Czuczwar

- Born: 7 May 1952.
- Master's degree: 1975 – Medical Academy in Lublin
- Doctorate: 1979 – Medical Academy in Lublin
- D.Sc. (*habilitation*): 1987 – Medical Academy in Lublin
- Professorship: 1992
- Currently: Vice President of the Polish Academy of Sciences, overseeing the Academy's Division V (Medical Sciences).

A corresponding member of the Polish Academy of Sciences since 2013. Head of the Chair and Department of Pathophysiology, Medical University of Lublin, and the Department of Physiopathology at the Institute of Rural Medicine in Lublin. A corresponding member of the Polish Academy of Arts and Sciences (PAU) since 2012. A member of the editorial board of *Pharmacology Biochemistry and Behavior* (Elsevier, since 1998) and *Neurochemical Research* (Springer, since 2014). In 2016 he joined the editorial board of the book series "Advances in Neurobiology" (Springer). In 2007–2010 he was head of the Polish Pharmacological Society.

He chaired the scientific committee of the International Congress of the Polish Pharmacological Society (Krynica, 2010). He organizes an annual conference on "Progress in Research on Epilepsy and Antiepileptic Drugs."

In his research he looks at interactions between antiepileptic drugs, in search of effective methods of treating drug-resistant epilepsy. He also studies how the ligands of different neurotransmitter systems affect the anti-convulsive and neurotoxic properties of antiepileptic drugs.

He has authored or co-authored 389 scientific articles (according to PubMed), cited a total of 7,967 times to date. His Hirsch index is 43 (citations and index according to the Web of Science). He has promoted 41 doctoral students, four of whom have gone on to earn D.Sc. (*habilitation*) degrees, and two the title of professor.

substance and it turned out to excellently augment the action of existing antiepileptic drugs. What is more, the blocking of other glutamic acid receptors, called AMPA, led to the synthesis of drugs now in use, such as topiramat and perampanel. And so, an idea that arose more than 30 years ago, trying to impede the stimulatory effects of glutamic acid, was first studied in animals, and then it led to the development of drugs that are now in use.

You spoke about synthetic molecules. Are plant-derived substances still being used in pharmacology?

Of course, pharmacology still draws upon those resources. One such promising substance used in treating epileptic seizures is resveratrol, obtained from the dried skins of red grapes. It helps eliminate free radicals, which are suspected of contributing to epileptic attacks. Eastern medicine – Chinese, Indian, and also Korean – is largely based on plant materials. In China, for example, there are hospitals that treat patients exclusively by means of plant-derived substances. Many of the substances contained in such natural medicines have been described and classified. Those that demonstrate neuroprotective action are tested in models of Alzheimer's disease, models of epileptic seizures, models of Parkinson's disease, and they often have promising action.

Pharmacology therefore faces newer and newer challenges and there is still a lot waiting to be discovered. We draw upon advances in chemistry, the ability to synthetically modify various chemical substances, and also look for substances among naturally occurring compounds. There is no shortage of inspiration, but unfortunately it takes some time before new drugs make it from the lab to the pharmacy shelves.

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