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Exploring Uncharted Areas of the Brain: The Endorestiform Nucleus

Dr. Wilner:
This is Clinician's Roundtable, and I'm your host, Dr. Andrew Wilner.

The study of neuroanatomy received an important boost with the introduction of Camillo Golgi's stain in the late 1800s. This new tool allowed neuroanatomists to visualize individual neurons as well as their axons and dendrites for the very first time. Our guest today is neuroscientist Dr. George Paxinos who, along with his team at the Neuroscience Research Australia Institute at the University of New South Wales in Sydney, has discovered a new anatomical structure in the brain using his own special stain for nervous tissue. Dr. Paxinos is the author of many books and more than 100 journal articles. Details of this new brain area are revealed in his latest brain atlas, Human Brain Stem: Cytoarchitecture, Chemoarchitecture, Myeloarchitecture.

Dr. Paxinos, welcome to ReachMD.

Dr. Paxinos:
Good morning, Andrew. Pleased to be here.

Dr. Wilner:
Before we delve into your discovery, I'd like to share something we have in common. You completed

your Ph.D. at McGill University just a few years before I arrived for my neurology residency at epilepsy fellowship. I wonder, was the famous neurosurgeon, Dr. Wilder Penfield, still working at the Montreal Neurological Institute when you were at McGill?

Dr. Paxinos:
He was working there, and I studied until one of his post docs, D.O. Hebb, Don O. Hebb, who was, when I arrived there, the Professor of Psychology—subsequently the Chancellor of McGill—and he actually influenced me as it concerns behavior, understanding how we can understand the behavior, how the components that produce intelligence, emotion are organized.

Dr. Wilner:
Yeah, I think those must have been very exciting days. Dr. Penfield, of course, was the one who mapped out the human homunculus in the brain.

Dr. Paxinos:
Yes, yes, legendary person. In fact, there is even a street, Dr. Penfield Street, in Montreal.

Dr. Wilner:
I lived on… My apartment was 1100 Dr. Penfield Avenue. How about that?

Dr. Paxinos:
(laughter) Right.

Dr. Wilner:
So, Dr. Paxinos, I want to learn about this new brain structure. I thought special stains were tools of the 1800s like the Golgi and the Nissl stains. How is it you came to invent a new stain?

Dr. Paxinos:
Yes. These were the classical stains, and I introduced to atlas making a new approach, a new stain—chemoarchitecture it is called—that is using the chemical phenotype of neurons that is as a criterion to define regions using what neurotransmitter they contain or what receptor they contained, what enzyme they contain. The brain is organized that way. The receptors or the neurotransmitters are not spread uniformly throughout the brain. They have regional distribution. Some areas have dopamine and have normal adrenaline, for example. And if you look just at these neuroactive substances, you can get a window into the brain to see how the brain is organized. And indeed, did we use Nissl, which is a very powerful tool, and Golgi, but chemoarchitecture is even more powerful because at a glance it gives you the organization of a region if the substance you are looking at is actually differentially distributed. And the brain looks as though it is a colored-in book already. You don't have to be a great neuroanatomist to identify a region not known before.

Dr. Wilner:
Well, it probably helps to be a great neuroanatomist. (laughter) Tell us about this new structure, the endorestiform nucleus. How big is it? What does it do?

Dr. Paxinos:
Well, it's about the size of a pea, and the function is not something that I am involved with. I just do the basic maps. I identify an island, for example. I say this is Tasmania, and someone else might go and check whether it is populated, whether there are forests there, there are animals, but I just look and set a basic plan. It's like Google Map without function, just the structure of the brain, which subsequently can be used by people who want to study either function or what neurochemicals it contains, whether it is present or not in a disease. They then have a better map to work with. There's an island there that they would pay special attention to, whereas before they didn't know anything was there.

It actually happened to us, too. I looked with a colleague of mine at the degeneration. That is where the fibrous projections from the spinal cord end up in the brain. In cases of therapeutic anterolateral cordotomy that the patients who suffer from terminal cancer and they were subjected to severance of some of the pathways of the spinal cord that lead to the brain in the hope of alleviating pain—the decompression by the way wasn't very helpful—but nevertheless, a colleague of mine and I looked at one of those brains, and we found that it was either terminal—preterminal degeneration that is a projection from the spinal cord to this region, but we didn't know its existence. In the map we made, we indicated that something was there, but we didn't say this is a nucleus. And it was when I connected it to a piece of information that is looking at the chemistry of the structure for an enzyme which breaks down acetylcholine, called acetylcholine esterase, and combine it with that information from the clinical case where the spinal cord pathways are shown to either end there or at least pass through there, that I thought "Well, this must be a different area." In other words, if you don't know something exists, you tend to ignore; you cannot report it. So we provide the structure of the anatomical, the topographic maps of the brain. Other people can then superimpose their information including function.

Dr. Wilner:
If you're just joining us, you're listening to Clinician's Roundtable. I'm Dr. Andrew Wilner, and I'm speaking with Dr. George Paxinos about his discovery of the endorestiform nucleus.

Well, Dr. Paxinos, let me follow up on that. You're telling me that your focus is descriptive and, of course, which is the first step. How did you get involved in creating brain atlases in the first place?

Dr. Paxinos:
Yes, I was interested in brain and behavior in the rats—I was studying psychology then at McGill—but I was frustrated in that there was not a good atlas of the rat brain. And when in a sabbatical at

Cambridge, I noticed this stain, acetylcholine esterase, how it showed the brain beautifully, that you could see the organization of the brain, the different areas in different colors and different shades of brown; then I would be able to do a better map, a more accurate map, both stereotaxically—that this will allow people to make interventions in the brain by reference to skull marks—and also internally to be more approximating reality, what really is there. I thought that we would only spend a year on this, but we were successfully constructing an atlas on the rat, and then I thought that maybe I'll spend a bit more time just on the human, and then I was—I spent a bit more time on development, and I haven't finished. I'm still constructing atlases, which are successful approximations that I hope they get better. If we look at the atlases, we did—the first atlas we did nearly 40 years ago, 39 years ago, and today you would find a lot of differences, and hopefully for the better.

Dr. Wilner:
Well, I understand that your atlas, The Rat Brain in Stereotaxic Coordinates, is one of the most often cited neuroscience references, so it sounds like you've succeeded.

Dr. Paxinos:
Yeah, it was rewarding that people use it. In fact, really, scientists, I think the greatest concern they have is the way they are perceived by other scientists, and citation is an index for that. The other thing that motivates us—Charles Watson and myself who have done most of this work together—is if we manage to find an area previously not known to science, such as the endorestiform nucleus. And if I could mention, Charles is a successful saxophone player, and when we luck upon a structure, then we stop and he plays the saxophone.

Dr. Wilner:
Nice. That's nice. So, do you think there are still any new discoveries to be made with the traditional white microscope?

Dr. Paxinos:
Well, yeah, a lot. In fact, it is far easier to identify things with a microscope, or as we do it, produce large prints, spread them in a large hole and walk through the brain—large magnification—so every section of the brain would be magnified to a tabletop size and that it's far more high resolution this way than looking at imaging. Imaging has some advantages over conventional stains, but as it concerns identifying regions in the brain, there is no comparison. The histology wins, a 100 times the resolution.

What we are doing now is still going back to histology. And, in fact, the important thing really is to get the tissue—in the case of humans, that's short period or small period, so that there are not changes in the brain, and the staining, the uptake of the stain, is high quality. And certainly we have work to do for a long while yet, and there are a lot of areas not identified yet in the human brain. In the brain stem, we

are satisfied that we have rehabilitated the human brain nearly to the point of our knowledge of the rat brain and the monkey brain, which we have studied intensely in optimal conditions because we can take the tissue straight after death. So, for the human brain stem, we are satisfied that we just about contributed what we can contribute, but for the rest of the human brain, there is still a lot of work to be done, but we have a prototype, and this is the Rhesus and the marmoset brains. The Rhesus probably might not have any differences with the human brain as it concerns the number of areas, nuclei—not even in the cortex, that is. The areas we studied in parallel we find all areas. We find in one, we find in the other as well, so we have a prototype to work with, so it is helpful. Once you know that the human should have this nucleus and you actually examine the human tissue exactly where you find this structure in the monkey brain, then you have a greater chance of actually finding it. What was unusual about the endorestiform nucleus which we recently identified is that we first saw it in the human—which, if you permit me, Andrew, to say here that given how much roomier the human brain is, well, the human brain is a good model for the rat.

Dr. Wilner:
I hope you do find some differences between the human brain and the monkey brain in your work. (laughter) Tell me, how would you counsel young physicians or neuroscientists who are interested in a career in neuropathology? What should they be thinking about, and which kinds of techniques offer really—are the wave of the future where they're going to make new discoveries?

Dr. Paxinos:
Yes, I think that histology is still quite good if you use the modern techniques of demonstrating the localization of neurotransmitters, receptors, enzymes, but also, the hybridization techniques—the Allen Brain Institute has done an excellent job with this—will reveal things that are otherwise understated in the conventional stains. But still, it would be… To my knowledge, that would be more powerful, far more than imaging.

Dr. Wilner:
One last question, Dr. Paxinos. Can you tell us about your next project?

Dr. Paxinos:
Yes. Well, we are interested in the dugong brain, and we are going to look at the brain stem—since all things brain stem are of interest to us—to see what is exaggerated in that species, because it actually gives you pointers to what might actually be the true organization of the human brain. What happens is these have different talons and exaggerate certain areas. The great insight we got on how the mammalian brain is organized was through studying the avian brain, the bird brain. And you might say, "Well, bird brain, why did you do that? Nothing good is said about the bird brain." We think birds have

first-class brains. They just have not had good public relations. And we have produced an atlas of it, which assisted us to identify, to delineate, segment the regions of the human and the rat brain better, especially in an area called the (inaudible)*14:32, which is far more strikingly evident what happens there in the bird than in the mammal where it's not clear what is happening there. But once you know what to expect, then you can also see it in the mammal.

So we are going different directions. We are also working on MRI atlases on, indeed, of the human brain stem—the Duke University, the laboratory of Al Johnson, who has the best, highest resolution images in the world—so we are starting with excellent material, and we will see what happens there. And with the advantage in that the MR images are not distorted—as it happens when you have histological sections that you pull through fluids that we get distortions—but the MRI, if it's in the skull, is even better, that its relations to the reference point of the skull remain true like histology. So there are advantages. Also, the data are inherently 3D, so you can display the information better, and you can do certain studies, connectivity in the MRI that you cannot do in histological tissue. So there are benefits, and we are trying to do this as well.

Dr. Wilner:
Dr. Paxinos, I am really impressed with your curiosity in pursuit of comparative zoology in showing us how it can be very revealing for the study of the human being. I think that's fantastic.

Dr. Paxinos:
Thank you.

Dr. Wilner:
Many thanks to our guest, Dr. George Paxinos, for joining us today and discussing his discovery of the endorestiform nucleus. I am your host, Dr. Andrew Wilner. To access this episode and others in this series and to download the ReachMD app, please visit ReachMD.com where you can Be Part of the Knowledge. We encourage you to leave comments and share this program with your colleagues. Thank you for listening