Schizophrenia, Imaging and Therapeutics
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I have chosen for you today the topic, "How antipsychotics work - attaching to receptors and changing reality." What I was hoping to convey to you is this very curious human condition called psychosis, and how we now attempt to treat it with medications. I wanted to lead to see what this thing is that we call psychosis, and how is it that it responds to given medications. In this talk I will introduce you to a patient because, as I have learnt, people have their own fantastic notions of what it is that psychosis is, but I actually wanted to show you what it actually is. I want to talk about what we used to do before we had effective medications. I want to talk about how these medications came about, and how they work, and perhaps leave you with some questions which we still have not answered.

What is psychosis? If you were to ask a normal group of people, you would come across ideas such as delusions, loss of contact with reality, fixated beliefs in something that isn't real, sensory deviations from the norm, hallucinations, imaging hearing or seeing things that are not really there etc.

Through these sorts of ideas, we are realising the complexity of what psychosis is. Medicine has had to standardise these definitions so that we are strict and appropriate in our application of them, because you cannot go and do a blood test or a brain scan and say "That was a delusion." It does not work that way. It does come out in a thoughtful interview, that you can decide whether someone has psychosis or not, and when you say someone has psychosis, it is usually because either they are exhibiting something we call delusions, and delusions are false, fixed beliefs, or they are having hallucinations, which is a false perception. Delusions are an idea, false and fixed. Hallucinations are a perception. So believing that the police is out to get you, if it is in fact not true, is perhaps a delusion. Seeing a policeman chasing you when no one is there is a hallucination. So these are these two important terms which are very commonly used in this area: delusions and hallucinations. They are not the same, but they are often commonly seen in people who are psychotic, because you could easily see a person who, first, delusionally believes the police is out to get them, but also, in their hallucinations, sees police officers chasing them when they are not there. This might serve as something of a quick definition. But that is an abstract definition. What does it actually look like when you talk to people who have that experience?

The easiest way to see this is to listen to the way that people with psychosis speak. This can be easily done by looking at some of the videos that we show to medical students or to people who are training in psychiatry. The first one we will consider was done in Montreal, Canada, and it is of a Doctor speaking to a middle-aged man of Afro-Caribbean descent, I think he is of Haitian origin. He is here talking about his delusions, which, in this case, are paranoid delusions. He is worried about people out to get him:

Doctor: Do you have some evidence that there might be some of those criminals??

Patient: Oh, trying to get me? Oh yes. Oh yes. But they don't know really whether I'm a fighter or a cop. This is what I hear all the time: he's not a fighter, he's a cop; he's not a cop, he's a fighter. I get this going all the time, but I keep my ears wide open because, in Montreal, I found out that the group that's around the area now, if they found out that I was in a car, they would phone ahead to somebody- god knows what they would do. My eyes and my ears are open all the time. My back - I keep watch all the time.

Doctor: And you feel that there is a kind of plot against you?

Patient: Oh yes, oh yes.

Doctor: Do you know who is organising it or??

Patient: Yes. It's a group from - it's an organisation from Alberta, from Calgary. It's an organisation out there. Like I went to an apartment, which I didn't know was the centre for this organisation, and I got in the apartment, and one of the guys downstairs came up and he says to this lady, he says, "What did you give him that apartment for" The guy's a cop!? She says, "Well, I didn't know." The other guy says, "Well, we don't have to look around for him. He's right here. That's pretty good." So I kept my eye on him, and the police was just outside at the door, so when they see me coming out, they started smiling because they didn't know themselves. This organisation is spreading around the kids, to people who don't know what they're talking about or people who just make things up. Like one person would say 'That's a fighter'. My god, down the line, someone will say 'Oh, that's Sugar Ray Robinson' or something like this, you know. It'll go from one person and it will build itself so high that god knows what's going to be in the head of some guy in a club that's running a business. The minute I walk into a nightclub, god, you can hear the bottles rattling. They're trying to get the old stuff off the shelves, you know, so I don't see what they're putting away.'

It is hard to get the entire story from this short passage, but if you listen to him over forty minutes, he will tell you that he is convinced that there an organisation out there that is plotting against him and that they are telling people that he is actually an undercover police officer, which of course he was not, but he was convinced that there was an organisation that is spreading this word around, so that is why, wherever he goes, people act oddly, they behave differently. So he talked, in the end, of how he walks into this pub or a bar, and he feels that they are putting bottles away because he was an undercover cop. The thing that I want you to note about it is that it is not that this is impossible. For instance, he could have been true tat he was an undercover cop (though, in this instance, it of course wasn't the case), but the more important thing is that what you often find about delusions is not that they are impossible, not that they could never happen, but they are just not true in this instance and are highly improbable.

Let me show you another example, in a very different setting, of a person who also has a fixed, false belief, but it is of a very different kind.

Patient: They are not biologically my parents.

Doctor: Right.

Patient: That is the fundamental truth in my life, that those two people, Mr and Mrs Tuba, are not biologically my parents.

Doctor: Your parents? You've been adopted?

Patient: I have not been adopted, no. This we never discuss it, we never talk about it. We just live in the house.

Doctor: If you're not adopted?

Patient: I live there.

Doctor: They brought you up?

Patient: They brought me up then, you could say that.

Doctor: But they haven't adopted you?

Patient: No. From age 12.

Doctor: Maybe you can help me understand what's going on?

Patient: From age one to 12, I had a very difficult life. I was tortured repeatedly. My mother was Anastasia Romanov, and my father really was Adolf Hitler. It's not that I'm making it up. I don't want to be sensational. He really was the Adolf Hitler of World War II.

Doctor: The leader of Germany?

Patient: Yes, yes. She knew that.

Doctor: Who is 'she'?

Patient: Anastasia.

Doctor: Mm. Anastasia Romanov is the daughter of the last czar of Russia?

Patient: Yes, czar, yes.

What is interesting about this so far is that these claims of hers would be rather easy to check against various sets of facts. However, the interview goes on in a very interesting manner in this respect:

Patient: Everything that I have to say cannot be checked historically because it's all behind closed doors. My knowledge and what I - I can name people, but it's all behind closed doors, and how can you verify it unless they come out and say yes? So you'll have to go through diplomatic channels. Quite possibly, they'll have reasons not to say anything, for national security mostly. So, now, Leonid Brezhnev knew of my existence. He knew who my mother was. He knew that I lived in Grenadier Road. So he's quite aware - he was very much aware of my existence. Now, he has since died, but he knew about my living arrangement in Canada, and when I went to the Soviet Union on a camping trip, in 1973, he did meet me, and I did have a chat with him. So he does-he knew of my existence.

Doctor: What did you talk about?

Patient: Afghanistan. This is before they invaded, and I said to invade.

Doctor: You told him to invade?

Patient: I told him to invade Afghanistan.

Doctor: Did you have a reason for doing that?

Patient: I had a reason, and he knew that. I said, if such and such a condition happens, if these events happen, there are two events, invade Afghanistan, so they must have happened, because they invaded Afghanistan. But it isn't just go and invade Afghanistan. It's just when ...

Doctor: Under certain circumstances?

Patient: These two things, if they occur, you have no alternative but to do it. It has a lot to do with spiritual and supernatural evil, which they are quite aware of.

These stories can go on, and every person who is afflicted by them has a different story to tell, so these stories are very individual. As you can see from these transcriptions of real interviews, they are very time-linked. These two people tell you very different stories, but both of them, we would say, would meet the medical definition of a delusion. The first person even reported some hallucinations - he said he could hear things about people talking about him and things like that. That is what psychosis is. Often people have what I would say is a rather extreme notion of disturbance; someone who is fighting and shouting. In fact this is very uncommon. For instance, although, I do not know the complete histories of these two people, it would not surprise me if never in their life had they ever done anything that would satisfy this idea of disturbing behaviour of raving or shouting. If you stood by them at a bus stop, you would actually have a pleasant conversation with them and nothing else, and you would have no other reason to suspect anything. Often, it is only when they feel free to talk about these things, with a psychiatrist or a family member or someone that they can trust, would they actually share these kinds of stories with you. So, I would say, the public perception or often the presentation of psychosis in movies and in sitcoms is often much more dramatic than its reality in real life, where it is actually not very uncommon. So, over the lifetime, anywhere from 1-4% of us may have experiences of these kind. For some, it may be time-limited; for some, it may be life-long. But it is not exceptionally rare, because 1-4% is a reasonable amount of people.

Now that you have a sense of what psychosis is, the question now is of what we have historically done with psychosis? Over the history of mankind, we have done many things and, sadly, most of them were barbaric until recently. Somewhere in the medieval ages, if you spoke like this and had delusions, one of the many things that might be done to you is you might be taken to a place where they put you in a barrel and spin you around. They did that because, during those times, one of the main theories about brain function was how the spirits moved around in your head. By the spirits, they meant the circulation of fluids in your brain, because, by that time, brain dissection had started, and if you just dissect a brain and only look at it with

naked eyes, what you can see are these big holes in the brain which are filled with fluid. So the idea at one time was that the reason why the people were having delusions and hallucinations was because these fluids were not moving around the brain properly, and to get them moving correctly, you had to spin the person.

About 100 years ago, when insulin was found for the very first time, some people experimented and observed that if you gave someone too much insulin, to where you created a state of coma in them, and then revived them back, you found that psychosis went away. So people had these theories that if you put someone into a deep sleep, all the would-be 'wrong connections' in the brain reset themselves somehow, and then, if you are able to bring them back, it is great because they would then be free of their delusions and hallucinations. It does not entirely work like that, but it is just one of the examples of the many things people have tried.

What else have people tried? Fifty years ago, in more humane environments, there was this idea of artificial hibernation. So, in around the 1950s, the scientists were very excited about the idea of how the brain works, and an area in the brain called the hypothalamus, and how you can put it into hibernation, and it resets the brain in some way. So, there were patients who were put in bathtubs that were full of ice chips, because the idea was to induce in you a state of hibernation. I am sure it induced in you a state of hypothermia more than anything else; the treatment really was not that good.

But interestingly enough, when all these efforts were going on, in 1951, in Paris, there was a drug company called Rhone-Poulenc, who were not really looking to make antipsychotics because, prior to the 1950s, no one ever thought that there could be a pill that could help you with these odd ideas and perceptions. At that time, it was seen to effectively be the same as me standing here today and proposing, 'You know what, let's make a pill for poverty.' In the same way, it did not make conceptual sense then to be looking for an antipsychotic drug. What this French company was looking for was a drug to calm people prior to and after surgery. The big problem in those days was that surgeons would do surgery, and as soon as the patient would come out of anaesthesia, they would be upset, they would flail around, and you can say that is no good for surgery. So, they were looking for drugs which would calm you down prior to and after surgery. Prior to that of course, they used alcohol or morphine, and both of them had side effects, so they were looking for an alternative drug. So, in the search for those drugs, this company happened to find this thing called chlorpromazine (RP4560). Of course, it was first discovered for use in anaesthesia so it was used by an anaesthesiologist, but he was very impressed by the calming properties of this drug. He found that people who have surgery would usually be very upset, but if you had given them this pills prior to their going into surgery, they actually came out very calm. So, he went over to his psychiatrist friends in Paris, and he suggested that they use it on their patients. That, in 1951, was the way these drugs came to be in psychiatry, and they had a dramatic effect in psychiatry.

It is hard for us to conceive those times, but to at least get some idea of this, we can get a sense of how things changed through the fact that in about 1950, there were about 40,000 people in asylums in and around London, 40,000. In the United States, there were half a million people in the asylums. But then, once these drugs were introduced, there is a rapid decline in the number of people who had to live their entire lives in asylums, with the figure for American dropping by four fifths, to 100,000 in thirty years.

Of course, the drugs were not the only cause in this sharp decline. There were also changes in society. There were changes in the way we view mental illness, in a positive sense. So, there were a number of factors that led to this, but the introduction of these drugs, which made it possible to control these systems, was absolutely central to this journey. But, regardless to the other factors, these antipsychotic drugs that began to be used in the 1950s were radical new treatments. But how do they work?

As I said, these drugs were not designed or discovered with an eye to help psychosis. We just got lucky when we found them. But once we had them, an entire brand of science tried to figure out how do these drugs work. It was clear that they worked through some action in the brain, but how precisely do they act in the brain?

It took them a quarter of a century before they began to get to the bottom of it. In 1976 the competing theories were resolved by Professor Phil Seeman, who was then at the University of Toronto. What he did was to take into account all the different antipsychotics that were being used in 1975, some twenty of them. Some of those drugs, you gave them in one or two milligrams three times a day. Some of those drugs, you gave them in 500 milligrams twice a day. So, these drugs were being used in all numbers, in all different ranges, and what he found was, regardless of what drug name, chemical class, structure it was, all these drugs bound to the same spot in the brain. So, a doctor could take all of these drugs, put them on brain slices, and they all bound to that one same spot. That was wonderful information, but what was an even more important finding was the way these drugs bound to that one spot in the brain actually predicted their clinical dose.

This told us that that spot in the brain was very important. But of course, when he discovered it in 1976, we did not know what that spot in the brain was. We just knew this was the spot where all the drugs' binds. Since then, a lot of research has been going on, and what it has showed us is that that particular spot, where all of these drugs went and bound, was a receptor in the brain. So, when I use the word 'spot', it is not just one region of the brain; actually, there are receptors in different regions of the brain, so wherever this receptor occurs, these drugs go and bind to it. This receptor was a receptor of a chemical called dopamine, and that was a huge breakthrough, because that, for the very first time, linked a psychiatric treatment to one precise receptor in the brain and thereby to one precise chemical. That was 1976.

Since then, we have learnt a lot about this receptor. We know it belongs to the dopamine system. We can even clone it now, so we know now exactly what the structure of this receptor is. We can even get the DNA of this receptor. So, we have made significant advances, but most importantly, we can actually now see this receptor. We do not have to go to brain slices anymore, as Phil Seeman had to do in the 1970s. We can actually image it in patients. But how does that work?

It happens through a technique of brain imaging called PET neural receptor imaging. It is a very complex technique and has got many steps in it, but in the end, what it creates for you is a picture that tells you the concentration of brain chemicals in different parts of the brain. This in effect tells you about the number of receptors in different parts of the brain.

I mentioned that all these drugs bind to that receptor, so what do you think would happen in someone who is taking medications which bind to that receptor and someone who is not taking medications? What you would expect is that, for those people who are taking medications, the medications will bind to the receptors, so the number of receptors that can be seen by the scanner will be much lesser, because they are occupied by the medication, and that is exactly what happens.

When you do a PET scan of a patient before they have antipsychotic medications, the scanner can see and display for you all the receptors that are in the brain, but when you treat the patient, the medication goes and it sticks to, it occupies, some of those receptors. Because those receptors are occupied, they cannot actually be seen by the scanner anymore, so the second time when you do the scan, you get the second kind of a picture, but what it tells us, in some ways, is the degree to which the drug has entered the brain, bound to those receptors and occupied them. We can measure the degree of binding, but most importantly, we can actually now start finding out the relationship between how much the drug is binding to those receptors and whether it is good and effective for the patient or whether it gives rise to side effects.

We have done some studies and what we have found is that if we knew in an individual patient how many of their receptors were blocked, we could actually predict whether this drug would work for them or not. Essentially, what we found was that if you block about 65% of the receptors, and more, people get better. If you block less than 65% of the receptors, people actually do not get better. So, this almost gave us a way of figuring out what might be the right dose for a particular person.

The other thing we learnt is that if you block too many of the brain receptors, if you block more than 78% or 80%, people start getting side effects. So now we learn that, in this particular condition, when using these kinds of medications, which work on this dopamine system, you need to block somewhere between 65% to 80% of the receptors, and if you do that, you will get a clinical effect and you will not get too many side effects. This information has been very useful in informing clinical care: it really makes a difference.

One practical impact of this has been that it has moved the doses that we use in psychiatry very much towards the lower end. So, one of the big critiques from the patients and their families often used to be that the medications left them sort of dopey and sapped in energy, and perhaps some of those complaints were right. Or, rather, those complaints were definitely right, but some of them were right in that the drugs were excessive. There has been a general trend towards lower doses, and there has been a general trend that, as the newer medications are introduced, this kind of brain scanning is now often being used to help find the right level of the medication.

So that has been the journey. We have talked about psychosis and what we used to do about it previously, how we learnt where these medicines work, how we identified the place in the brain where they work, how we can now image that place in the brain. What we cannot do, at the moment, is image every single patient. So if you go to a psychiatrist today and you have one of these conditions and he decides that your treatment needs to be with, let us say, Haldol or some medication like that, he is unlikely to send you to a scanner and then give you the medicine, and then look at a brain picture, and then tweak your dose - not that it would not be useful, but because it is not feasible or cost effective. In other words, there are much more sensible ways,

now that we know all of this information, to adjust the dose in the single patient, and these scans are too costly, too expensive, too cumbersome, to do them for everyone, but they have been very important in that they have helped us learn the principles of how to get this right.

So, what do we know now? We know that antipsychotics, which were discovered almost by accident about sixty years ago, work in the brain on the system called the dopamine system, on the D2 receptors. We also know that it is not just enough to give the drug; you must block a certain number of those receptors. So, if you give the drug but you are giving it at a dose that only blocks 10-40% of the receptors, you will practically see no results. You may falsely consider that this drug does not work for the person when you actually just did not get the right brain effect. What we have also learnt, which you might say is almost commonsense, is that if you block too many receptors, you get side effects - no surprise there, but what has been helpful to know is that that number is about 80%, so it tells you that there is a window with these drugs: somewhere between 65-80% and you have it right.

We know these things, but we still do not know some very important things. Why do some patients not get better even though we block the receptors? That is a big mystery. When this work in scanning started, we knew that these drugs did not work for a lot of people, and we thought that perhaps the reason for this was because they did not get into the brain and they are not attaching to the receptors, so if we found a way to get it past the blood brain barrier, these people would also get better. However, although that would have been a nice, elegant explanation, that is not the case. So, for most people, if they are taking the medication and they are getting the right levels of it, the drug does get into the brain, it does block the receptors, but some people still do not get better, and we just do not understand why this is - we have several theories as to what might be the case, but we do not know for sure.

The other very interesting question, which in many ways crosses the sort of brain/mind divided, is that that lady was quite convinced that she was Hitler's daughter - why should giving someone a pill change their mind about whether they are Hitler's daughter or not? To adequately answer that question, we would need one unified theory that encompasses brain function and belief formation. Then you can talk about how changing one can change the other. But at this point in time, I am afraid that we do not have any such comprehensive theory.