

THROUGH THE ILLUSIONS

By Edwin H. Rydberg

Instituto di Ricerche di Biologia Molecolare P. Angeletti SpA (IRBM)
Via Pontina Km 30600
I-00040 Pomezia (Rome)

“I've been here before,” thought John Smith. The same white stucco walls behind him, the same carefully manicured plants lining well-swept walkways. Most importantly, the same tinted, one-way windows on his left. Why did he let her bring him here? He didn't need some quack telling him things he already knew. He felt like a laboratory rat, as if every movement were being carefully scrutinized by a team of cold-blooded clinicians. He sat very still.

“They're watching you.” A voice, like a whisper on the wind, echoed through the still air.

“I know,” he answered in his own hushed whisper, quickly turning left, then right. Of course there was no one there – there never was. But still he looked.

Twenty-two. That's how old he was when he first heard them. The haunting voices. At first he had thought they were his friends playing pranks. But then they came when he was alone. Afraid that he would be locked up in an asylum, he had kept quiet as they grew more frequent. Gradually he stopped talking with his friends, finding that he was often unable to distinguish between their voices and the voice in his head – reluctant to run the risk of being wrong. He remembered turning to smoking as a way to relax, and found that it helped.

“What will you do?” The voice was louder now, appearing to echo from inside his skull.

“Leave me alone,” he said aloud, waving his arm through the air, as if he could disperse the voice. Then, quickly he sat down, aware that he was being monitored, and angry at his loss of control.

“Let me think,” John said to himself, as he pulled out a pack of cigarettes he had carefully hidden, and extracted one with a practiced flick into his fingers. He lit it and took a long, slow drag, savoring the deep calm and clarity it gave him. Things didn’t seem so bad while he was smoking.

* * *

“What’s he doing, doctor?” Jennifer Smith asked the white-coated man beside her.

“He’s responding to a voice only he can hear – an auditory hallucination.”

“He’s crazy?” she said – too loudly, she realized – as her voice echoed down the sterile hallway.

“Please, Mrs. Smith, ‘crazy’ is not an accurate or constructive term to use in this day and age. Your husband has a psychiatric disorder...” he began.

“Then the tests are finished, you have the diagnosis?”

“Yes, I just received the final results. Your husband is schizophrenic.”

“You mean he has several personalities?” The fear of living with Dr. Jekyll and Mr. Hyde flooded her imagination.

“No, Mrs. Smith. That’s a common misconception. Schizophrenia is not a multiple-personality disorder. It’s more of a disorder that affects reality perception.

Commonly, those afflicted will have hallucinations, delusions, or will simply withdraw from their surroundings.”

“Why, doctor, why did this have to happen to him?” she asked, anger and sadness welling up in her at the unfairness of it all. They stood silently, watching her husband smoke his cigarette to the filter. She still remembered him as her high school sweetheart; fun, caring, ambitious. Then, shortly after their marriage, he began to withdraw. She feared he was losing interest in her, that he had found someone else. Then she saw him arguing with himself.

John flicked the butt to the ground and reached into his pocket for his almost-empty pack.

“Understanding a person’s behaviour is arguably the most difficult challenge in science today,” the doctor began, clearly trying to add some meaning to a difficult situation. He continued slowly, as if looking for sure footing while crossing a muddy river. “Not only are there so many myths clouding the issue, but the little we do know suggests that the biological aspect is incredibly complex and involves the interaction of many different components.”

“The biological aspect?”

“The two largest factors in your behaviour – how you react to certain circumstances – are your environment: where you have lived, how you were raised, what friends you had, etc. and your biology: the predisposition towards certain behavioural characteristics that may be coded for by your DNA. And to be honest, we don’t even understand yet how important each of these factors is in the development of behaviour.

But there are certain situations where we can find genetic links – changes in a person’s DNA – that correlate with certain behavioural patterns.”

“Like schizophrenia?” she asked.

“Yes,” he responded. “Aberrant psychological behaviour, like schizophrenia, provides us with an obvious target, and we can then search through family histories for genetic markers, abnormal DNA patterns, that correspond to occurrences of the disorder. I don’t want to get your hopes up, Mrs. Smith – it will be some time before we understand the biology of schizophrenia well enough to think about a cure – but there has been progress.”

She turned back to the window and watched her husband. He had lit up another cigarette and was puffing away calmly, while staring at the plant in front of him.

“I wish he wouldn’t smoke so much,” she said, almost to herself. With everything else happening, the last thing they needed was for him to get lung cancer.

“It might seem strange, but smoking may be a clue to at least part of the cause of schizophrenia,” the doctor said, startling her out of her contemplations.

“How could that be?” she asked.

“Well, it seems that the incidence of heavy smoking is much higher in Schizophrenics, 80-90%, than it is in the general population, which is about 30%. This has lead to the suggestion that schizophrenics may be attempting to use cigarettes as a form of self-medication.”

“What do you mean?”

“Almost a third of schizophrenics report that they intentionally smoke to reduce their symptoms,” he answered.

She turned and stared in disbelief at the doctor.

“How could cigarettes help schizophrenia?” she asked.

He paused for a few moments, clearly trying to collect his thoughts.

“The answer to that will take a little explaining,” he began. “Our body is made up of countless cells, as you have probably heard. Picture each cell as a complex factory. But these factories are enclosed in a wall, or cell membrane, and would not be able to communicate with each other – as is necessary for our survival – if they didn’t have special ‘doors’ in the walls. Some of these doors are called channels, or specifically, ligand-gated ion channels, because they only function when interacting with specific molecules – their ligands. These channels cause a signal to be brought from outside the cell to the inside, to trigger a change in the cell’s functioning. When they make contact with their ligand they open, like the iris of a camera, and allow ions like sodium, potassium or calcium ions, for example, to pass into the cell. Different ligands open different channels, although more than one ligand may open the same channel. The opening of the channel results in a signal telling the cell to do something new.

“For example, at the neuro-muscular junction, where nerve cells contact the muscle cells, the nerve cells may release a signal molecule called acetylcholine. Acetylcholine crosses the space of the junction and binds to a channel, the acetylcholine receptor, which then opens, resulting in a signal that causes the muscle to contract. These junctions are found throughout our body, and the full receptors are constructed – a bit like Lego – from a relatively small number of different blocks, to fine-tune their properties. Different forms of the channel are found at different junctions. However, one such Lego block is called $\alpha 7$. Alpha-7 is found throughout the brain and nervous system.”

“But how does this relate to changes in DNA?” Jennifer asked.

“Well, over the last decade, many genetic studies of families with a history of schizophrenia have been performed, and the most consistently detected genetic differences are alterations in the gene for $\alpha 7$. These differences in DNA can result in a variety of changes to the $\alpha 7$ channel, anything from structural changes that would affect its function, to a reduction in the number of channels that each cell produces, which would decrease the efficiency with which the cell receives the neural signal.”

“And how would that cause schizophrenia, doctor?” she asked.

“Unfortunately, I can’t answer that Mrs. Smith. While we can understand possible ways that $\alpha 7$ can be affected in schizophrenia, we don’t yet understand why $\alpha 7$, itself, is particularly important.”

Jennifer Smith stood quietly, trying to take in all the information. It was a lot to grasp, but she thought she was getting a handle on it. One thing still puzzled her, however.

“Doctor, I still don’t understand how this is related to my husband’s smoking?”

“Ah, yes. Well, interestingly, $\alpha 7$ is one member of a family of receptors that, in addition to their biological ligands, also bind nicotine and are thus called ‘nicotinic receptors’. In some cases, such as with $\alpha 7$, nicotine may be more than ten times as effective at binding and activating the receptor as acetylcholine is. So, high levels of nicotine could help to restore a certain degree of normal function to the cells that are lacking in $\alpha 7$ acetylcholine receptors.”

“So, now you can see that a small change in your husband’s DNA can not only be responsible for the onset of schizophrenia, but also can explain his chain-smoking. And

I'm sure you can appreciate how complex the link between genetics and behaviour can be, and why it is so difficult to understand and cure disorders such as schizophrenia," he said.

* * *

It was peaceful in the hospital atrium. The voices had been silent for some time so John could just sit and enjoy the fresh air amidst the well-groomed plants. He heard the door open behind him.

"Hi, John. It's time to go back in." It was Jennifer. He stood and gave her a welcome kiss, suddenly aware that he had been smoking heavily. She hated it when he smoked.

"Sorry," he said. "It helps me relax."

"I know, and I understand." He could tell that she meant it.