Thoughts of a retired scientist: an interview with Martin Raff

Martin Raff is an Emeritus Professor at University College London (UCL), where he worked for more than 30 years on various aspects of immunology, cell biology and neurobiology until his retirement in 2002. In this interview, he recounts the thrill of his first few years in science, and discusses his current fascination with the fast-moving field of neuropsychiatric disorders.

Martin Raff was born and educated in Montreal, Canada. In 1968, he arrived at the National Institute for Medical Research, in Mill Hill, London, for what he expected would be 2 years of lab experience before continuing his career as a neurologist. However, the influence of a wonderful mentor and a series of quick and exciting discoveries encouraged him to change his plans and take up a research position at UCL, where he was funded by the Medical Research Council (MRC) for the remainder of his career. He made significant contributions to many areas of biomedical research, particularly cell biology and neural development. He is known as an outstanding mentor and educator, and he has also co-authored several textbooks, including multiple editions of Molecular Biology of the Cell. He keeps an office in the MRC Laboratory for Molecular Cell Biology at UCL and continues to contribute to science and science policy through participating in multiple scientific advisory boards in the UK and United States. He has also developed a special interest in neuropsychiatric disorders, and particularly autism.

Were you interested in science as a young person?

No, not at all. I was not a typical budding scientist in my youth. As a child, I was mainly interested in sports. Later, the Vietnam War is what led me to pursue a career in science.

I was half way through my medical neurology training in Boston, when they changed the US draft law. It was at the height of the War, and the change meant that immigrant physicians became draftable until age 35; before that, it had been 26. There were no options for a drafted immigrant. You couldn’t join the Public Health Service or the Reserves. I was dead against the War and refusing to serve if I were drafted would have meant going to jail. So, I went back to Canada with my family, turned in our Green Cards, and returned to Boston the next day as exchange visitors, allowing me to finish my neurology training.

Then, I had to decide what to do. I had originally planned to become an academic neurologist in the US, which meant I should spend some time doing research in a lab. I knew nothing about science, and so I asked the first friend I met what he would recommend I do. He suggested immunology, as that’s what he had done at my stage. After a quick phone call, he’d organised a position for me in an immunology lab in Paris. I didn’t really know what experimental immunology was, but I thought this sounded like a great plan!

A week or so later, however, a physicist friend of mine sent me an article that had been published in Science, called ‘Immunology at Mill Hill’. It seemed exciting: although I couldn’t understand much, it sounded like Mill Hill was the centre of the immunological universe. Plus, I’d visited London many years earlier and loved it. My friend who had fixed me up in Paris said that my chances of being able to work at Mill Hill were slim, as so many budding scientists wanted to work there.

But I pursued it anyway. I picked a person whose science I could understand least well, and I wrote to him, thinking that it would increase my chances, as others might also have trouble understanding him and be put off from applying to work with him. And this worked! He wrote back and offered me a place.

This was Av [Avrion] Mitchison, who turned out to be the perfect mentor for me in every respect. He gave me a project and set me free. He was a very eminent immunologist, and Mill Hill was a fantastic place to learn science. I knew nothing when I arrived, but my colleagues generously taught me how to do things, and within a few months my experiments were working; by 6 months I’d made a discovery. Remarkably, Av refused to put his name on the paper, even though the project had been his idea, and, by the time I arrived in London, he’d already begun raising the antibodies that I needed. Because of his generosity, and because this early discovery was important, I became an internationally known immunologist within my first year in science.
What did you discover in your time at Mill Hill?

At the time, it was just becoming clear that there were two distinct classes of lymphocytes — T cells and B cells — which had different functions. But the problem was that they looked the same and were all mixed up in the peripheral lymphoid tissues; there was no way of distinguishing or separating them to study their individual development and properties. Av had heard the American immunologist Arnold Reif describe an antigen called theta, now called Thy1, that was on the surface of mouse thymus lymphocytes, and Av hypothesised that it might also be present on the surface of T cells, which are derived from thymocytes. It turned out that he was correct, and it was pretty easy for me to demonstrate it.

Now that I had an antiserum that recognised mouse T cells, I wanted to visualise directly the antibodies binding to the T cell surface. To do this, I used a sandwich technique, where I added the anti-Thy1 antibodies, followed by fluorescent anti-immunoglobulin (lg) antibodies that allowed visualisation of the binding of the first antibodies in a fluorescence microscope. In my control, where I left out the anti-Thy1, the anti-lg antibodies on their own labelled a second population of lymphocytes, which turned out to be B cells, which had Ig on their surface that functioned as receptors for antigen. It was just a complete fluke that this control experiment identified these receptors and provided a marker for B cells. So, within the first year and a half, we had cell-surface markers that distinguished T cells from B cells, which allowed us to separate and study the two cell types. We then just went after the lowest-hanging fruit!

Another thing we discovered in the course of these experiments was that the binding of anti-lg antibodies to B cells was localised at one pole of the cell. This was in contrast to the binding of anti-Thy1 antibodies to T cells, which was all over the cell surface. I was very excited about this discovery and started looking more closely at the Ig on B cells to see if I could find some markers that distinguished those cells from white blood cells, which were all mixed up in the peripheral lymphoid tissues. I found that the Ig on B cells was all over the cell surface, and I also found that the Ig on T cells was all over the cell surface. This was a big discovery, as it showed that proteins can diffuse in the plane of a membrane and that ligand binding can redistribute them and remove them from the cell surface. They not only had implications for how lymphocytes respond to antigen, but also provided evidence for the fluid nature of cell membranes, with implications for how cells in general respond to extracellular signalling molecules. These experiments took me from immunology into cell biology — entirely by chance.

All of this happened very quickly. So little was known in those days that almost every experiment led to a discovery. My first 2 years in science were by far the most productive of my career, whether measured by publications or the importance of the discoveries. From then on, it was downhill, which is somewhat depressing, but it was such a thrill to live through those early days!

**What made you decide to leave clinical medicine for good?**

In the first 2 years, I had no administrative responsibilities and could focus on doing experiments and publishing papers, and I loved it. It was so different from medicine. You were trying to find out how a little bit of the world works. It wasn't competitive in those days, and you could publish your results reasonably quickly in good journals — very different from how it is now. Even so, I still considered myself to be a clinical neurologist and thought I would go back to America. Then, Av was offered a prestigious Professorship at UCL, and, one evening in the pub, he said that, if I wanted to stay in science, he would be pleased to have me move with him to UCL. Until then, I had never crossed my mind that I would give up medicine and become a full-time scientist, but I decided that night that I would. That was the best decision of my life!

Av and I then wrote a Programme Grant proposal to the MRC to do what I'd done in the immune system — that is, try to produce antibodies that would distinguish different cell types in the nervous system. That was the plan. Looking back now, it was an incredibly naive proposal, but the MRC funded it. Kay Fields, who was a molecular biologist, joined the group and took on the project. She induced tumours of the rat nervous system with a carcinogen, isolated cell lines from them, immunised various types of animals with the cells, and absorbed the antisera with various non-neural tissues. This seemed a reasonable approach, as tumours usually arise from a single cell. But it turned out to be incredibly difficult to produce an antisera that could distinguish one tumour cell line from another, or even one that could distinguish neural cells from white blood cells (for reasons that are still not understood). After a number of years, Kay finally produced one antisera that specifically labelled the surface of Schwann cells in cultures of rat peripheral nerve cells. This provided the first proof of principle that we could make antibodies that distinguish a neural cell type. Jeremy Brookes, who had joined us as a postdoc from Harvard, used the antisera to purify and study the properties of Schwann cells. Around this time, Kohler and Milstein discovered a way to make monoclonal antibodies, which helped us find markers for cells in the rodent central nervous system. At last, we were on our way and could start making some contributions to neurobiology, especially the development of glial cells.

**These days, you've got a special interest in autism spectrum disorders [ASDs]. There's a lot going on at the moment: what would you say has been the most important recent advance?**

My interest in ASDs has come from having a grandson who is autistic. The neuropsychiatric disorders are at last emerging from the darkness into the light, and, in some respects, the ASDs are leading the way. Progress has come largely through human genetics and mouse models based on these genetic studies. Once you have identified a big-effect mutation that substantially increases the risk of developing one of these disorders, you can often create a mouse model of the condition, where it is possible to study the underlying neurobiology. This strategy is really opening the field up and changing the way we think about these disorders.

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There are several findings that stand out for me. One came from Thomas Bourgeron at the Pasteur Institute, who showed that mutations in genes that encode cell adhesion proteins (called neurelins) that work mainly...
at synapses can confer a major risk for ASDs. That was strong evidence that a problem at synapses could contribute to ASDs. My guess is that synaptic problems underlie many, if not all, neuropsychiatric disorders.

Other remarkable findings have come from studies of monogenic disorders that often display the core features of autism, as well as other neurological signs. These include, for example, Rett syndrome, tuberous sclerosis, Fragile X syndrome and neurofibromatosis. There are now excellent mouse models for these disorders, and, in every case I’m aware of, if you fix the problem in the adult brain – either by correcting the genetic defect or by using a drug that corrects a problem in a downstream signalling pathway – you correct most of the phenotype in the adult mouse. This was completely unexpected, because these are considered developmental brain disorders, which, in part, they are. But, these findings indicate that a large part of the clinical problem, in the mouse models at least, reflects reversible functional defects in the adult brain, which is very good news. The findings indicate how remarkably plastic the adult brain is, which explains why we old geezers can still learn.

In terms of human genetics, there have been several important advances. Whereas it was initially thought that a combination of large numbers of common genetic variants (polymorphisms) underlie most ASDs and other neuropsychiatric disorders, there is increasing evidence for the importance of rare mutations that greatly increase the risk of these conditions. It is now estimated that mutations in hundreds of different genes can substantially increase the risk of developing an ASD, and, so far, no individual gene when mutated contributes to more than 1% of ASDs. Thus, even though ASDs are common, affecting about 1% of the population, most individuals with an ASD are likely to have a rare, or even unique, underlying genetic predisposition. Moreover, so far, none of the big-effect mutations are specific for ASDs, as the same mutation can predispose to different neuropsychiatric disorders, even in the same family. With the rapidly decreasing cost and increasing speed of DNA sequencing, it is now possible to sequence exons or whole genomes on a much larger scale than before, which will greatly accelerate the hunt for neuropsychiatric risk genes.

What’s the outlook for clinically treating neuropsychiatric disorders?

It’s useful to distinguish the neuropsychiatric disorders from the neurodegenerative disorders. In the latter, nerve cells degenerate and die, and the diseases are progressive. In neuropsychiatric disorders, by contrast, nerve cells don’t seem to degenerate or die abnormally, and the disorders are generally not progressive. Huge resources have gone into studying neurodegeneration, and there’s been a lot of progress, but the news has been largely depressing. For the neuropsychiatric disorders, however, the news is much better, as I mentioned earlier. Also, as we come to understand these disorders better, I think we’ll understand more about normal human brain function than we have learned from studying neurodegenerative diseases. For example, in bipolar disorder, which affects about 1% of people, we know what the problem is: there is a defect in the mood control system. But we know very little about the normal mood control system. If we can identify a big-effect mutation that greatly increases the risk of bipolar disorder, it could provide a molecular handle to help understand not only the disorder, but also the normal mood control system. It might make it possible to create a mouse model with which to figure out what part of the brain, what cell types, and what synapses and circuits are affected. You can also make pluripotent stem cells from the models and from patients with the genetic defect, and make the cells and the synapses and the circuits to study the defect in vitro. These approaches will eventually tell us what the normal mood control system is. In studies of ASDs, human genetics and mouse models hopefully will eventually tell us something about how the social brain works.

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How close are we to translating basic research into treatments?

These are still early days, but there are reasons to be hopeful. For example, there are clinical trials going on in Fragile X syndrome. In this disorder, the mutation leads to decreased production of the FMR1 protein, which normally inhibits the translation of certain mRNAs at synapses. Thus, the FMR1 deficiency leads to excessive production of the proteins that the mRNAs encode, one of which is the glutamate receptor mGluR5, which is normally involved in certain synaptic plasticity responses. As mentioned earlier, there are excellent mouse models of Fragile X, and there are now drugs that inhibit mGluR5. In one study, treatment of young adult Fragile X mice with this drug reversed almost all of the serious neurological and physiological defects within weeks. A preliminary short trial of a small number of adult Fragile X patients with a different mGluR5 inhibitor suggests that the drug may have beneficial effects in a subset of patients. More human trials are underway, so we should know soon if the encouraging results in the mouse models will also be seen in humans.

What would you say are the most important outstanding questions in this area?

In the ASDs, I think it is crucial to try to understand why so many different mutations predispose to the core features of autism. It will also be important to determine where the abnormality starts, and what features then follow as downstream consequences. One thing that all people with ASDs have is a strong attraction to sameness: they don’t like change and are attracted to things that are predictable. People are unpredictable, which may be why individuals with ASDs prefer things to people and therefore socially disconnect from people. As Harlow showed in the 1960s, when monkeys are socially isolated from other monkeys from birth for 6-12 months, they display severe autistic features when they are reintroduced into their monkey colony. Thus, it may be that people with ASDs socially disconnect because of their drive for sameness, and this then leads to a reinforcing feedback loop that sustains the autistic behaviour. If an addictive attraction to sameness is the root of the problem, we need to understand the underlying neurobiology of this addiction.

I also think that regression is important in autism. About 25% of people with ASDs show dramatic regression in their second year, and most of the others lose one or more social skills that they had acquired. Such
losses provide an opportunity to understand the underlying neurobiology in ASDs. For example, both girls with Rett syndrome and mouse models of the disorder undergo dramatic regression, and both display severe breathing irregularities when they regress. This provides a golden opportunity to study the physiological changes that presumably occur in the respiratory centres in the brainstem at the time of regression. It might be possible in this way to connect a physiological change to a simple quantifiable behavioural change – something that is so far missing in the field.

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Any advice for young scientists?
I think it is important to recognise that it is a privilege to be a professional scientist. It’s always been amazing to me that I was paid to work in a lab to try to figure out how a bit of the world works. I would have paid to do it! But, it’s equally important to realise how hard it is to be a successful scientist. Most experiments don’t work, and so you have to be driven by curiosity in order to keep going. It has become even harder these days, because there are so many more scientists than in my day, and so it is much more competitive, especially now that the funding for science has flat-lined or decreased in many places.

The real currency of science is discovery, so you should choose mentors and environments that maximise your chances of making a discovery as early as you can. It’s unfortunate that the common view is that papers are the currency of science. Discoveries also cheer you up and remind you why you are doing science. Ideally, you should aim for an environment where you can chase unexpected observations, but you need to have a nose for which observations are interesting and worth following up. That’s hard to teach, but, if you’re in a good environment, there will be colleagues around to talk to about your findings and ideas, and it’s crucial to be able to tap your environment in this way.

Another challenge facing young scientists is that information is increasing exponentially, but brain size is not. Just to stay current in any area, you could spend most of your time on a computer. This means that there’s far less time to think hard about what you’re doing: what am I trying to find out? How can I kill my current hypothesis? We should encourage PhD students and postdocs to take time off on a regular basis just to think about their project; it is inefficient to wait until it’s time to write a paper or thesis.