Raff *BMC Biology* 2010, **8**:42
http://www.biomedcentral.com/1741-7007/8/42

BMC Biology
incorporating Journal of Biology

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QUESTION & ANSWER

Video Q&A: What is autism? - A personal view

Martin Raff*

Martin Raff talks on autism.

Martin Raff trained in Medicine at McGill University and was a Resident in Neurology at Massachusetts General Hospital when in 1969 he became fascinated by the nascent field of cellular immunology and abandoned medicine to join the laboratory of Avrion Mitchison at Mill Hill, London and subsequently at University College London, where he made seminal contributions in the biology of T and B lymphocytes. Later, he turned to developmental neurobiology, which occupied him until his retirement from active research in 2003.

It was only after his retirement that he became interested in the biological basis of autism, when it affected his own family. In this interview, he talks, as a biologically knowledgeable grandparent, about how he sees the disorder and where he thinks research on the condition is leading.

*Correspondence: m.raff@ucl.ac.uk
MRC LMCB, University College London, Gordon Street, London WC1E 6BT, UK

Edited transcript

Your research has been in immunology and neural development. What got you interested in autism?
I have a grandson who's autistic, and that's the immediate reason. But I did train in neurology many years ago and what's interesting is that in those three years I never saw a patient with autism, which was very rare then. And then I was a developmental neurobiologist for 25 years and I never heard a talk on autism, even though it was thought to be a brain development problem: there wasn't a single talk in 25 years, which is quite remarkable. Now autism has increased greatly in prevalence and is frequently in the news. But it was my grandson, who is now 8, who got me interested in the subject.

What are the defining features of autism?
The three core features are a problem with social interactions, which is often the heart of the matter; a problem with language; and a tendency to have restricted interests

and repeated, stereotypic motor behaviors. That is the so-called autistic triad, and you need to have two of the three and to develop them by the age of 3 to be considered autistic.

Is autism just one thing? – Isn't it a spectrum?

It is a spectrum, and probably the reason, or at least one important reason, for the apparent increase in autism is that the diagnostic criteria have expanded enormously. At the bad end of the spectrum are the classic autistic kids, and at the best end of the spectrum are Asperger kids, who have much less trouble with language and are often very smart. But there is also everything in between. I'm sure you have many colleagues with some features of autism.

You have an unorthodox view of how autism develops – What is it?

I'm not so sure it's unorthodox. It starts from the need to explain the basis of the autistic triad: why do these features occur together in this way? Besides the three core features, there are also often other associated features - seizures in 30%, intellectual impairment in 50% and behavioral abnormalities such as temper tantrums and feeding and sleeping disorders, and so on, which are often found in addition to the core triad.

So I think a major question is what binds the core triad together? There is no part of the brain that I'm aware of where an abnormality would explain this triad while leaving so much else intact.

A simple possibility would be that there is a fundamental problem in the interaction between the child and its parent, usually the mother. It has been known for many years that if this interaction is seriously disturbed - if you can't achieve what's called joint attention with your mother or care giver - then you don't learn to speak, you don't learn social skills, and you develop restricted interests and, not infrequently, repeated stereotypic movements.

Is there any evidence for this view?

Yes. If a monkey is separated from its mother and other monkeys at birth, it becomes autistic: it doesn't develop normal vocalizations or social skills and shows restricted interests and repetitive motor activities such as rocking. If a child is born deaf, for example, and it is a year or two or three before that's picked up, the child has an increased likelihood of developing autistic features; or if a child is born blind and this is missed, that too is often associated with autistic features. And children who are brought up in orphanages, particularly the big orphanages where you don't get one-on-one care at all, as occurs in some Romanian orphanages, for example, these kids often develop what's called institutional autism. So I think it's pretty clear that if you interfere with the child-parent interaction (and other social interactions), this can lead to the autistic triad.

Are you saying it's all the parents' fault?

Kanner, when he first described autistic behavior in 1943, noted in his report that the parents of these children were cold and didn't seem to have an interest in people; you can see that he was thinking of blaming the parents. Then Bettelheim picked up on the idea and argued that it really is the parents' fault and talked about refrigerator mothers. So during the 1950s and 1960s, it was commonly felt that autism was an emotional disorder and parents were to blame.

Do you think they were wrong?

I think they were right in pointing to the child-parent relationship as a problem, but they were pointing to the wrong part of the relationship. It is the child that is abnormal, largely for genetic reasons. Autism is the most genetic of the neuropsychiatric disorders. So the child seems genetically impaired in his or her ability to interact, and the question is what is the nature of the impairment. There are lots of ideas about this. One is that autistic children don't process faces normally, which interferes with their interactions with people. Another is that they don't have the special interest in biological as opposed to inanimate things that normal children have. And another idea is that they can't figure out what's going on in somebody else's mind - called mind blindness or a 'theory of mind problem.'

I think it is very unlikely that any of those are the primary problem. I think a more likely explanation is that there is a problem with attention - a particular type of attention problem. There's increasing evidence that these children have what's called sticky attention, which is a problem with attention disengagement. When autistic children are focused on something, it's very hard to disconnect them and get them to focus on something else. So shifting attention from one thing to another seems to be a problem.

Is there evidence for 'sticky attention'?

I think the best evidence for that comes from Landry and Bryson. They published a paper in 2004 on a study of 5-year-old toddlers - 30 autistic, 30 Down syndrome, and 30 neurotypical, matched for IQ, who were taught to focus on an image on a central computer screen. The images were just abstract shapes falling through space. Then a different abstract image was put up on one of two lateral screens, and the child's eye movements were tracked electronically to see how they quickly looked at the new image. If the image on the focus screen was removed at the same time as the new image was put up, the autistic kids performed as well as the other two

groups, but if the focus image was left on when the new image appeared on a lateral screen, then 20% of the autistic children didn't look at the new image at all, and, of those that did, many were slow to do so, compared with the other two groups. In these experiments, there were no people, no faces and no social interactions, suggesting a fundamental problem with attention, and, specifically, a problem shifting attention from one thing to another.

My grandson had this problem in spades. He developed quite normally for a year and a half and then, starting halfway through his second year, over a period of weeks, he dramatically regressed: he stopped looking at you, stopped talking, and you could no longer get his attention. He could be looking at a wheel spinning or a train going round a track or water falling, and you could poke him in the arm, flash a light in his eyes, yell in his ears - but you just couldn't get his attention. It's not that he wasn't paying attention - he just wasn't paying attention to you.

There is a lot of interest in the genetic analysis of autism - What do you think genetics has to offer?

Well, as I said, it's the most genetic of the neuropsychiatric conditions, and so genetic studies are likely to be the best route to understanding the underlying neurobiology. There are already about 15 genes that have been implicated in autism. At the extremes, there are two classes of genetic influences in multifactorial diseases like autism. There are polymorphisms, which are common genetic variants that increase your risk a bit, usually less than 1.5-fold. These are generally identified by genome-wide association studies using SNPs (single-nucleotide polymorphisms) and, for the most part, have not been very informative in autism.

The other class consists of rare mutations that greatly increase your risk and are much more informative. Thomas Bourgeron, for example, was the first to identify *neuroligin* mutations in some individuals with autism. He guessed that there might be abnormalities in synapses in autism, and so he looked at two genes, *neuroligin 3* and *neuroligin 4*, which encode proteins that work only at synapses, sequencing the protein-coding regions of these genes in more than 100 autistic individuals in multiplex families (that is, with 2 or more autistic members), as well as in a comparable number of neurotypical individuals. He found two Swedish families - one with a *neuroligin 3* mutation and the other with a *neuroligin 4* mutation: in each case, one brother was autistic and the other was diagnosed with Asperger syndrome. That was the first direct evidence that a mutation that affects a protein that works only at synapses can lead to an autism spectrum disorder and that the same mutation in the same family can lead to both ends of the spectrum. This was a giant step forward. Subsequently, mutations in genes that encode proteins that interact with neuroligins at synapses, including neurexin and shank proteins, have been found to predispose to autism and other neuropsychiatric disorders. I suspect that synaptic defects may be at the heart of the problem in many of these disorders and that defects in many different genes can probably contribute to different disorders.

There are some single-gene disorders, like Rett's syndrome, fragile X, and tuberous schlerosis, in which autism is part of a more complex neurological syndrome. These are therefore called syndromic forms of autism. There are very good mouse models of these, which are proving to be very informative. It seems to me that a promising way forward in autism, and in neuropsychiatric disorders generally, is to start with a big-effect mutation in individuals with the disorder and then try to model the disease in an experimental animal such as a mouse. Then you can make use of the powerful tools available in mice to try to find out what is responsible for the abnormal phenotype: which part of the brain, which types of neurons, which synapses, and which circuits.

Could the very widely publicized connection between vaccination and autism account for the increase in incidence?

This of course has been an enormous public concern, particularly for parents or grandparents who have autism in the family. Interestingly, in the UK the concern is with MMR (mumps, measles, rubella) vaccination, whereas in the US the concern is with the mercury compound (thermasol) in the vehicle.

I should have said earlier that dramatic regression occurs in about 30% of autistic kids (although minor regression occurs much more commonly): they develop apparently normally for a year and then in their second year they lose what they had and become classically autistic. After that, they may slowly recover to a variable extent, and some may recover completely. So you can imagine that, if you have a child that's fine but then, two or three weeks after a vaccination, he or she stops looking at you and stops talking, it will be difficult to convince you that this has nothing to do with the vaccination.

But there have been ten or more studies that show pretty unequivocally that vaccination is not involved in the autism spectrum disorders. One of the best was from Denmark, which showed that the prevalence increased about 15-fold from 1990 onwards, yet MMR was introduced in Denmark in the 1970s, and thermasol was removed in the 1990s with no apparent impact. So I think it's safe to say that vaccination is a red herring. Autism spectrum disorders are now recognized to be a fairly common condition, affecting almost 1% of children, and so there will be a substantial number of coincidences in which vaccination seems to trigger the condition.

So the question remains why there has been such a large increase since 1990. It is still unclear if there has been a real increase, because there are a number of other possible explanations that could account for much of the increase. One is that the diagnostic criteria have broadened enormously since 1990. Another is that parents, teachers, and doctors are much more aware of autism today than they were before, which is a big factor. Another is that, in the 1990s in America, many states provided special educational support for autistic children, so that parents were keen to have the diagnosis confirmed to take advantage of these services, which no doubt contributed to the increased prevalence, as well as to a decrease in the stigma associated with autism, which, in itself, would greatly increase the number of diagnoses.

To go back to genetics - How do you get from a rare mutation to the cause of the disorder in the common cases?

Now that you can sequence DNA increasingly cheaply and quickly, it is feasible to sequence the genomes of large numbers of autistic individuals, which almost certainly will uncover increasing numbers of rare, big-effect mutations that contribute to the disorder. Once such a mutation is identified, one can try to produce the condition, or a part of it, in an experimental animal such as a mouse, where you can analyze the neurobiological basis of the problem. Once this has been done, which could take years, it will be necessary to go back to the humans with the same genetic problem to find out if the same cells, the same brain regions, the same synapses, and so on are involved.

One way to do this is to make induced pluripotent stem cells (iPSCs) - first from the mouse and then from autistic individuals with the same genetic problem. iPSCs closely resemble ES (embryonic stem) cells, in that they can proliferate indefinitely in culture and be induced to differentiate into almost any type of cell in the body, including into different types of neurons. Fortunately, developmental neurobiologists are rapidly figuring out how to get many different types of neurons from such pluripotent stem cells. Once you have figured out how to get the appropriate types of neurons, you can let them form the synapses and circuits, either in a culture dish or after transplantation into a developing mouse brain, to show that you can reproduce the physiological defects that you found in the mouse mutant. Then you would be ready to produce iPSCs from the autistic humans and use what you had learned studying the mouse iPSCs about how to produce the relevant types of neurons, synapses, and circuits that you think are affected, to see if you can reproduce the same type of physiological abnormalities. If you succeed, you can screen for drugs that can correct the problem and see if they can ameliorate the clinical problem. All of this will be difficult and very time-consuming, and it may not work, but, if it did, the payoff could be great, both in terms of new drugs and what it could potentially tell us about how the normal human brain works. I am optimistic, especially as many of the mouse models of the syndromic forms of autism have been shown to be at least partially reversible by treatments given to adult mice; this suggests that many of the clinical problems may result from reversible functional defects in the adult brain, rather than from irreversible anatomical defects that many believed to be the problem.

Where can I find out more?

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Published: 12 April 2010

doi:10.1186/1741-7007-8-42
Cite this article as: Raff M: **Video Q&A: What is autism? - A personal view.** *BMC Biology* 2010, **8:**42.