The search for autism's roots

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A marked rise in the number of people diagnosed with autism sparked controversy over the safety of certain vaccines. As the furore dies down, Kathleen Wong talks to researchers seeking the real causes of this unsettling condition.

In child-development circles, it is known as the new epidemic. Anxious parents are flooding clinics with children who won't speak, who scream at the touch of clothing on their skin and who seem locked in a world of their own. The diagnosis is autism.

In the mid-1970s, autism was seen as a rare condition, thought to affect between two and four children in 10,000. But recent studies suggest that the figure has grown, on average, by 40% (ref. 1). Most autism researchers think that changes in the way the condition is defined and diagnosed lie behind the rise in recorded cases. But that is of little consolation to the parents of children with autism. They want to know what is happening to the minds of their children and whether anything can be done to treat the condition.

Hopes that these questions will be answered are now higher than ever. New technologies are offering deeper insights into the way the autistic brain functions, and advances in molecular biology promise to unearth the disorder's genetic roots. Meanwhile, educators and therapists are discovering that, if caught early, children who would have been institutionalized just 30 years ago can now stay with their families and attend mainstream schools.

Under analysis: studies of brain activity are revealing the ways in which the minds of children with autism process information (top), and therapy is helping to improve the children's social skills.

Unusual behaviour

Autism can seem a somewhat paradoxical disorder. Around three-quarters of all people with autism are mentally retarded[2], but a small fraction have considerable mathematical or artistic abilities. Some are insensitive to pain and have a tendency to injure themselves; others are hypersensitive to touch. People with mild forms of autism can have strong verbal skills, whereas those with more severe forms are unable to speak at all.

Underlying these behaviours are problems with social interaction and communication and a tendency to take an obsessive interest in particular subjects. The first two features of autism can appear at a very young age. Babies with autism seem to lack the innate preference that normal babies have for looking at faces rather than other objects[3]. They fail to develop the skills needed to understand the subtleties of facial expressions, a vital part of face-to-face communication. As they grow older, children with autism act as if they are cut off from the world. Researchers using brain-imaging techniques have found that these children process visual information about faces in the same part of the brain they use to process information on objects[4] — most people use other, specialized, brain regions to perceive faces.

In addition, children with autism seem unable to guess what other people might know or are thinking by studying what they say and do. 'Sally–Anne' scenarios used by psychologists highlight this deficit. In one example, Sally and Anne are playing together. Sally places a marble in a covered basket and leaves the room. Anne then moves the marble from the basket to a box. Most children with autism think that when Sally returns, she will look for the marble in the box[5] because they cannot view the situation from Sally's perspective. Normal children can anticipate Sally's behaviour because they have a 'theory of mind', which usually develops at around age four[6]. But many children with autism never develop such an understanding.

Individuals with autism also have a tendency to focus on details, rather than the big picture. Such children might concentrate on the colour of a utensil rather than its shape, preventing them from learning the difference between a fork and a spoon. This love of detail can, in a few rare cases, result in extraordinary talents — Stephen Wiltshire, a British artist with autism, is famed for his ability to produce beautifully detailed sketches of complex buildings.

Recognition that a range of symptoms is associated with autism has forced psychia-

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Simon Baron-Cohen suggests that autism may be an exaggeration of gender differences.

trists to change the way that they define the condition. Classical autism, first defined in the 1950s, is now seen as part of a spectrum of related conditions. The latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), published by the American Psychiatric Association, recognizes five additional disorders, such as Asperger's syndrome, as part of the autistic spectrum of behaviour. People with Asperger's syndrome typically show many of the social impairments seen in autism, but with less severe deficits in language or cognitive skills.

These diagnostic changes may explain the rise in the number of recorded cases of autism. Studies conducted in Japan, the United States, Britain and Scandinavia[7–10] show a rise in the number of cases over the past 45 years.

But take into account changes in the way the condition is defined, and the figures do not seem so disturbing. The first epidemiological studies, conducted in the 1960s and 1970s, used narrow definitions of autism that excluded individuals with milder forms of the disorder. The earliest definitions also omitted mentally retarded children who may also have had autism. "It would be very surprising indeed if the broadening of the criteria for autism weren't the major part of the explanation," says Michael Rutter of the Institute of Psychiatry in London.

Increased public recognition of the disorder is also likely to have contributed to the apparent epidemic. As parents and doctors have become more familiar with the disease, the chances that they will identify potential cases and refer them to psychiatrists have increased. The rising number of children attending nursery schools, where they get more attention than at other stages of their schooling, may also play a role, as a child's social deficits tend to stand out from the behaviour of its peers.

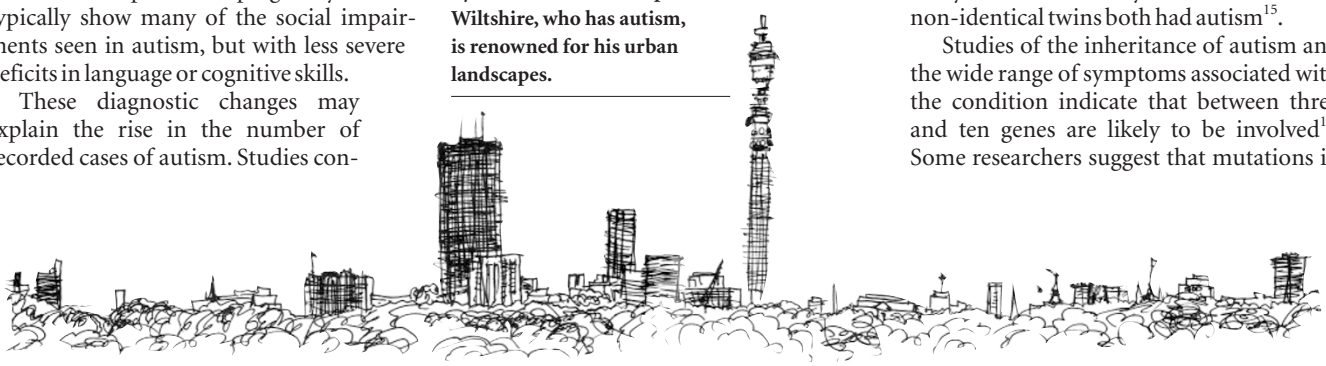
Increased awareness

The growing consensus that changes in diagnosis and public awareness are behind the rise in recorded cases came as a relief to public health officials responsible for vaccination programmes. In 1998, Andrew Wakefield, a gastroenterologist at University College London, proposed a novel and terrifying connection between autism and the combination measles–mumps–rubella (MMR) vaccine[11]. He described the cases of 12 children who appeared to be developing normally until they received their MMR shot between the ages of 15 and 18 months. Soon after, the children developed a kind of inflammatory bowel disease, began losing basic speech and social skills, and were subsequently diagnosed with autism.

The theory found a ready audience among parents and the press. Around half of all children later diagnosed with autism appear to develop the symptoms very suddenly, around the time that the MMR jab is

STEPHEN WILTSHIRE

Eye for detail: artist Stephen Wiltshire, who has autism, is renowned for his urban landscapes.



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Not guilty: the idea that the MMR vaccine might give rise to autism has now been rejected.

administered. These children regress severely over a period of six months, losing social skills that they had begun to master. The fact that the vaccine first went into widespread use in the 1980s, when studies suggest that incidence rates for autism started to climb, added credibility to the claim.

Subsequent studies have failed to find a link between MMR and autism[12–14]. On closer analysis, the data from several parts of the world show that the rise in autism actually started before MMR, Rutter explains.

But just as the MMR controversy is dying down, another potential vaccine-related cause for autism has been highlighted. Many vaccines use a mercury-containing preservative called thiomersal. Fears that vaccinations may be exposing children to dangerous levels of mercury have led the US Institute of Medicine to schedule a meeting for next month to discuss possible links between thiomersal and autism. Most researchers doubt that thiomersal will turn out to play an important role in the autism story, but they want to settle the issue to head off another vaccine scare.

Despite lingering fears over the safety of vaccines, many researchers believe that the real key to understanding autism lies in sufferers' genes. Studies of twins offer the most convincing evidence of such a link. One study found that if one identical twin has autism, the other twin has a 60% chance of developing the condition, and a 92% chance of having a condition within the *DSM*'s spectrum of related disorders. In non-identical twins the odds of the second twin having an autism-spectrum disorder fall to 10%. The study failed to find any cases in which two non-identical twins both had autism[15].

Studies of the inheritance of autism and the wide range of symptoms associated with the condition indicate that between three and ten genes are likely to be involved[16]. Some researchers suggest that mutations in

more than a threshold number of these genes could cause classical autism, whereas fewer mutations would result in social shyness or delays in acquiring language skills.

The search for 'autism genes' has yielded some promising leads. Links have already been established with abnormalities on chromosomes 7 and 15 (refs 17–20). Many researchers are confident that at least one gene for autism will be identified within the next five years.

But the fact that the identical twin of a child with autism may not develop the condition suggests that environmental factors are also involved. Mutations to one or more autism genes may, for instance, increase a child's vulnerability to an unknown environmental trigger encountered during early infancy or in the womb.

Other researchers are searching for physiological signs associated with the disease, some of which seem to develop before birth. Autopsies of people with autism have revealed abnormalities that would have developed by around 30 weeks after conception[21]. In particular, structures in the brain's limbic system, responsible for emotions, aggression, sensory input and learning, appear to be underdeveloped.

A more low-tech analysis is also shedding light on developmental factors that may be linked to autism. Children with autism tend to have ring fingers as long as or longer than their index fingers[22], as do their family members — an attribute that has been linked to high testosterone levels in the womb[23].

This finding also bolsters the 'extreme male-brain' theory of autism[24] put forward by psychologist Simon Baron-Cohen and his colleagues at the University of Cambridge. Baron-Cohen argues that many symptoms associated with autism are magnified versions of the normal gender differences between men and women. Men are known, for example, to be better at spatial tasks than women. Individuals with autism and those with Asperger's syndrome score even higher on these tasks than normal males. A similar trend is seen across a range of behavioural and biological attributes known to be linked to gender, from the size of particular areas of the brain to the age at which children acquire language skills. Baron-Cohen says that the theory is attracting attention from within the autism research community, but that it is too new to have been fully evaluated.

Other groups are looking for correlations between specific types of autism and mutations in potential autism genes. Gerard Schellenberg, a neurologist at the University of Washington in Seattle, and Geraldine Dawson, director of the university's Autism Research Center, are studying families in which at least two siblings have autism. The researchers aim to diagnose the specific types of autism the siblings suffer from and to link the symptoms to anomalies in their DNA.

Despite autism's complexity, researchers are confident that they will eventually understand it.

New therapies may eventually be developed from these studies. In the meantime, therapists are using what they already know about how the minds of children with autism function to design behavioural treatments.

Improved interaction

The most successful therapies focus on helping children with autism overcome their behavioural and communication problems. One example is the 'pivotal skills' programme developed by education researcher Robert Koegel of the University of California, Santa Barbara. The programme teaches children to ask questions instead of screaming for attention, and to respond to the salient features of an object, such as number and suit on a playing card, rather than the irrelevant details, such as a crease in the card's corner. Koegel motivates the children by choosing lessons suited to their interests, for example by teaching an animal-obsessed child to use terms for the difference between big and little by going to the zoo and comparing a rabbit and an elephant.

A lack of controlled studies makes it difficult to compare Koegel's programme with other behavioural approaches, but anecdotal evidence suggests that the system works well. "Even if they don't recover completely, they are overcoming the biggest problems," says Koegel. He now hopes to begin studying the neurological changes that take place in the children's brains as they learn, and to match different therapies to different types of autistic disorders.

Early-intervention programmes such as Koegel's, along with the research into autism's causes, have raised hopes that autism may one day become a treatable condition. Despite its complexity, researchers are confident that they will eventually understand the disorder. Teasing out the genetic and environmental causes is a tricky task, but the many strands of research on this most baffling condition could come together over the next decade. ■

Kathleen Wong is senior editor of *California Wild*, the magazine of the California Academy of Sciences.

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Pen pals: with therapy, children with autism are able to participate in mainstream schooling.