Autism – an evolving concept[†]

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Background The rapid increase in research endeavour has not kept pace with the advent of well-publicised theories and treatments for autism.

Aims To explore some of the newer developments in biological research into autism.

Method A review of recent publications and presentations.

Results The concept is shifting from the narrow perception of aloof autism, described by Kanner, to a wider one that includes a spectrum extending to a broader, subclinical phenotype. The genetic basis has been established; now we need to discover the location and interaction of the relevant sites. There is considerable interest in the bowel as a pathogenetic agent, particularly in the effects of exogenous opioids and multiple viral infection (the latter posing a public health problem). Also of concern is the role of (potentially treatable) epilepsy, analogous to the Laudau–Kleffner syndrome.

Conclusions In the absence of a cure, the implementation of ideas will continue to outstrip factual evidence. Clinicians are challenged by the availability of information (and misinformation), particularly on the internet.

Declaration of interest None.

Autism was only identified in 1943, and only in 1971 was it distinguished from schizophrenia (Kolvin, 1971). Soon recognised as a genetically based biological disorder (Rutter, 1998), its position in developmental psychiatry parallels that of schizophrenia in general psychiatry in validity and severity. About 80% of people with autism have significant learning disabilities (mental retardation). Conversely, among people with learning disabilities, autistic traits are rife (Bhaumik *et al*, 1997), with the full syndrome occurring in about 17% overall, rising to 27% of those whose IQ is less than 50 (Deb & Prasad, 1994). This gives autism a central place in the psychiatry of learning disability, where its recognition often brings understanding to otherwise inexplicable behaviour. The sharply rising volume of published research highlights the limits to our knowledge not just of autism but of the normal structure and functioning of the nervous system. This review focuses on some of the areas, particularly in neurobiology, that are changing our perception of this disorder, as well as some of the present public preoccupations which psychiatrists have to face.

DIAGNOSTIC CATEGORIES AND SUBTYPES

Since the tower of Babel, language differences have blocked progress. A major achievement has been the alignment of diagnostic criteria in the latest revisions of the *International Classification of Diseases* (ICD–10; World Health Organization, 1992) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–IV; American Psychiatric Association, 1994), coupled with the development of effective and internationally recognised research instruments for autism – the Autism Diagnostic Interview (le Couteur *et al*, 1989) and the Autism Diagnostic Observation Schedule (Lord *et al*, 1989). Autism is not a diagnosis to be made lightly; an assessment requires several hours. The group that developed the Handicaps, Behaviour and Skills Questionnaire (Wing, 1996) has just released an updated and expanded instrument, the Diagnostic Instrument for Social and Communication Disorders (DISCO). Although it is too soon to judge its place, it is certainly no briefer than the original; consequently, until shortened forms are available, it is likely that the shorter and well established Childhood Autism Rating Scale (Nordin *et al*, 1998) will retain its place in everyday clinical practice for identifying the less equivocal case.

The concept of autism, and consequently its diagnostic criteria, continues to evolve. For example, one of the original members of Wing's definitive triad of symptoms, 'limited imagination', has been re-defined and the existing criterion of 'restricted, repetitive and stereotypic behaviour' is being challenged (Tanguay *et al*, 1998). The loss of the latter criterion would leave autism defined by defective social communication but might also make it indistinguishable from a dissocial personality disorder. The appraisal of other symptoms, such as abnormal perception and conation, is hindered by their subjective nature.

Milder and more subtle characteristics are being recognised in the relatives of those with full-blown autism – the 'broader phenotype' (Bailey *et al*, 1998*b*). As symptoms are dimensional rather than categorical entities, the result is a continuum that entails uncertainty as to where the cut-off from normality actually falls. Although this leaves the core disorder untouched, it encourages the inclusion of a much wider population under the diagnosis. The effect will be to change our perception of autism, particularly in areas such as outcome and the need for specialist resources. As a result, and coupled with a greater public awareness, autism is becoming less of a specialist topic and more an everyday subject for mainstream services. Despite evidence that the prevalence of core autism remains constant (Fombonne *et al*, 1997), there is speculation that an increase, perhaps in subtypes, may be taking place, for reasons which vary from selective immigration (Arvidsson *et al*, 1997) to measles, mumps and rubella (MMR) immunisation (Wakefield *et al*, 1998*c*). This possibility is not easy to test, because changing criteria, increased awareness and the recognition of subtler variants make it hard to maintain a constant diagnostic threshold. It is especially difficult

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in certain groups such as those where a profound learning disability obscures or mimics the syndrome. Outside developmental psychiatry other diagnoses may be made, particularly of obsessive–compulsive or dissocial personality disorders, or even schizophrenia.

Asperger syndrome has been demarcated as potentially distinct from autism. It was initially defined by the presence of useful speech, normal ability and clumsiness, but in 1992 ICD–10 restricted it to those in whom there was an absence of early speech delay. The question of whether the two disorders are really separate or simply the poles of a single continuum echoes other psychiatric debates. It has proved difficult to assemble a series of cases on the new criteria, controlling for both age and ability, but those studies that have succeeded suggest that there are differences in cognitive profile, social interest and, perhaps, abnormal preoccupations (Kugler, 1998). Some characteristics, such as motor incoordination and delay, have proved elusive (Ghaziuddin & Butler, 1998), while other potential criteria, such as the qualities of insight and humour and the desire for social interaction, have been suggested.

DIFFERENTIAL DIAGNOSIS

An essential component of the definition of autism is to identify what it is not. The relationship with schizophrenia is far from being resolved, particularly as the latter comes to be seen as a developmental disorder (Keshavan, 1997) with characteristics parallel to and overlapping those of autism. The issue is clouded by the occurrence of psychotic symptoms which may exist transiently as part of an adjustment reaction or may reflect the concrete and literal thinking or the social incomprehension that make up autism. Follow-up of people with autism suggests that there is no major association with schizophrenia (Volkmar & Cohen, 1991). However, confusion stems from the spectral nature of both disorders, with milder or incomplete phenotypes being recognisable in relatives. Wolff (1995) identified a schizoid disorder in 2% of those attending her child psychiatric clinic and subsequently equated the disorder with Asperger syndrome. About 5% of these children, 12 times the expected rate, had developed schizophrenia by the age of 27 years. A dissection of the relationship between schizoid disorders, schizotypal personality disorder and schizophrenia highlights the difficulty in distinguishing pre-psychotic schizophrenia from an autistic disorder (Watkins *et al*, 1988; Wolff, 1995). Other disorders, such as catatonia and simple schizophrenia, can be teasingly indeterminate: are they variants of schizophrenia or do they represent an autism that has either had an unusually late onset or merely come to notice with adolescent deterioration? While diagnosis must take account of the developmental trajectory of the disorder, it is likely that resolution must await genetic studies of the two spectra, autistic and schizophrenic.

There is a risk of the diagnosis of autism being extended to include anyone whose odd and troublesome personality does not readily fit some other category; such over-inclusion is likely to devalue the diagnosis to a meaningless label. For the same reason, it is important to remain alert to the possible existence of other diagnostic groups. Newson has identified such a group with the label of pathological demand avoidance syndrome after its predominant characteristic. Children in this group have, at most, a mild learning disability and a high degree of social awareness, although many have enough in common with autism to attract the diagnosis (Newson & Maréchal, 1998). Pathological demand avoidance syndrome forms a long-standing and expensive disorder, persisting into adulthood and posing considerable problems in its management. The description is based on a series of 200 children but replication has been hindered by the lack of more formal publication.

Autism and epilepsy

Epilepsy occurs in up to 30% of those with autism and can amplify their symptoms. There is much to suggest that epilepsy might cause or mimic autism. For example, behavioural changes similar to those of autism can occur in the Laudau–Kleffner syndrome (acquired epileptic dysphasia) in which clinical seizures may be absent in as many as 30% of sufferers, the diagnosis of epilepsy being based on an electroencephalogram (EEG). It is difficult to know the significance of the paroxysmal activity that has been found in the sleep EEGs of 50% of children with developmental dysphasia, even where there is no history of seizure (Picard *et al*, 1998). A similar figure has been obtained for autism (Kawasaki *et al*, 1997). A paroxysmal EEG has a statistical association with autistic regression, the emergence of autism after a period of apparently normal development (Tuchman & Rapin, 1997). However, a paroxysmal EEG is present in only a minority of the children, being more frequent the later the regression (Chez & Buchanon, 1997). Such results raise the possibility of an epileptic basis for some cases of autism and of using the EEG as a routine investigation. This is not something to be done lightly. A recording would need to include both light and slow-wave sleep, which can be difficult to achieve. Furthermore, it is only justifiable where the results might affect clinical management: it is difficult to dismiss a paroxysmal abnormality as an epiphenomenon that, in the absence of seizures, might be ignored. Yet treatment is far from straightforward, with only five published cases where autism has responded to an anti-epileptic drug, usually valproate (Gillberg & Schaumann, 1983; Nass & Petrucha, 1990; Plioplys, 1994). Nevertheless, in some of these cases the disorder had been established for up to a decade, and it is possible that better results might be obtained with earlier, more vigorous or more persistent treatment at a younger age and by exploring a wider range of drugs, possibly including steroids. The last may be treating some other or more fundamental process. A successful response was reported in a six-year-old child who had developed autism at 22 months (Stefanatos *et al*, 1995). In the absence of seizures or any focal or paroxysmal EEG abnormalities, steroids were given on the basis of an abnormal auditory evoked response. Treatment trials (whether using antiepileptic drugs or corticosteroids) will be hampered by the difficulty of enrolling children soon after the onset of the disorder.

Any evaluation of outcome needs either some form of untreated comparison or a better picture of the natural history: which children show autism from birth, which deteriorate in early childhood, how abruptly and in what areas of function. In particular, how often is there a clear autistic regression? These data need to be related to the outcome, for we need to know which are the children who will improve, particularly shortly after onset. Early remission may have meant that they failed to reach the psychiatrist and the diagnosis of autism. Others may have been segregated as suffering from disintegrative disorder, an overlapping group with a boundary that is becoming increasingly indistinct (Mouridsen *et al*, 1999). Earlier identification

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should come with greater public awareness – something that the Checklist for Autism in Toddlers (CHAT) might bring (Baron-Cohen *et al*, 1992). The CHAT promises to be a very specific primary care screening instrument, but one that is very insensitive when used within the first two years of life.

COMORBIDITY

It is becoming more apparent that autism has familial links with other psychopathology, notably depression, obsessive–compulsive disorder and motor tics (Bolton *et al*, 1998). Depression is more frequent in the immediate relatives and pre-dates the arrival of the child with autism. However, its occurrence is linked to the development of depression in the child with autism (Ghaziuddin & Greden, 1998). In the background are abnormalities of serotonin chemistry; while these are not specific to autism, there appears to be a common thread linking these disorders to each other and to the drugs affecting serotonin transmission, including risperidone (McDougle *et al*, 1998) as well as the antidepressants (DeLong *et al*, 1998).

The relationship of autism to learning disability is confusing. The increase in the prevalence of autism with increasing severity of learning disabilities leads to the following questions. First, how far does autism, which produces early social and communicative deprivation, cause learning disabilities? Second and conversely, can learning disability, with its widespread deficits, result in an autistic presentation – is there a real distinction between 'severe learning disabilities with autistic features' and 'autism'? Third, are some of the medical disorders that cause learning disabilities particularly likely to produce autism?

Most studies have looked at populations with either learning disabilities or autism, rather than controlling for both. Hence, the high prevalence of autism in Cornelia de Lange syndrome probably reflects the severity of learning disability associated with that disorder (Berney *et al*, 1999). Once social anxiety had been disentangled from social impairment, fragile-X syndrome did not appear to have a greater claim on autism than other disorders producing similar degrees of disability, although it is associated in its own right with a pattern of behavioural symptoms which has some similarity. Tuberous sclerosis is linked and – although the combination of epilepsy and severe disability may contribute – the association also appears to relate to the siting of the tubers (Bolton & Griffiths, 1997).

THE PATHOLOGY OF AUTISM

The failure to find an anatomical or physiological basis for so discrete a syndrome as autism has been particularly frustrating. Recent enthusiasm for cerebellar and brainstem dysfunction (Courchesne, 1997) gets some support from the delineation of a cerebellar cognitive affective syndrome (Schmahmann & Sherman, 1998) which includes many features common to autism, including impaired executive functioning, difficulty in modulating social behaviour and language difficulties. The assertion that, in autism, there is vermal reduction or enlargement (Courchesne, 1995) remains controversial and unconfirmed, the debate centring on whether the age, ability and gender of the subjects have been adequately taken into account. In the end, the issue is whether autism can be explained by cerebellar pathology occurring early in development. More recent post-mortem results confirm earlier findings of a reduction in cerebellar Purkinje cells and abnormalities in brainstem nuclei. They also indicate a much more inconsistent and widespread abnormality, with diffuse cortical involvement rather than one localised to the limbic system, cerebellum or brainstem (Bailey *et al*, 1998*a*). Megalencephaly is frequent and fits with the clinical observation of a head circumference above the 98th percentile in about one-fifth of people with autism (Fombonne *et al*, 1999). However, the prevalence of this phenomenon will depend on whether comparison is being made with the newer norms which show an overall increase in population head size (Cole *et al*, 1998).

Another area that lends itself to exploration is the effect of motivation on the ability to initiate automatic (as opposed to voluntary) behaviour. The ability to perform fluently only when relaxed or very aroused (whether from fear or excitement) is well recognised and may relate to cerebellar function. This forms the basis for facilitated communication that, although effective (Simon *et al*, 1994), is so inconsistent and unreliable as to be discredited.

As neuroimaging improves so does its potential as a powerful research tool. Better definition allows the measurement of volume rather than just cross-sectional area. Still new is the measurement of the proportions of the brain – of ratios (of one functional area to another) rather than absolute values. Such ratios are likely to be gender-specific and to vary over time and with developmental phase. They may well identify syndromic differences, although the scope for permutation might reduce this to a numerological hunting-ground.

As promising as neuroimaging is functional magnetic resonance imaging, which can pinpoint an area by the changes in blood flow that accompany activation as the subject attempts various tasks – tasks that are being increasingly tightly defined (Baron-Cohen *et al*, 1997). It is this precision which holds out the most hope of relating clinical attributes to their neurology and physiology. One result might be to show some tangible distinction between various clinical subtypes, not just Asperger syndrome and high-functioning autism, but also other groups such as those characterised by repeated violence, compulsive routines, and the various forms of sociability (Attwood & Wing, 1987).

Positron emission tomography, using labelled compounds, can track the uptake of specific neurotransmitters, while magnetic resonance spectroscopy allows the measurement of the concentration of individual compounds. An example is a pilot study that has shown a localised abnormality of the metabolism of the prefrontal cortex which correlates with the neuropsychological and language deficit of autism (Minshew *et al*, 1993).

Magnetoencephalography identifies electrical changes by their effect on the magnetic field rather than the smeared voltage changes of the conventional EEG. Its very high temporal and spatial resolution promises to deliver what brain mapping could not.

The use of these newer investigative techniques will be limited by their expense, the skills required for valid and reliable results, and the level of cooperation and consent needed for what may be a demanding procedure.

AETIOLOGY

Genetics

The obscure inheritance of autism has meant that genetic explanations have been

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slow in coming, while a parade of environmental factors have been held responsible. Many of the pathogenic mechanisms proposed as causing a secondary autism are more likely to be environmental stressors bringing out a genetic vulnerability. Twin studies have shown that, while autism is a discrete disorder, its inheritance is probably multi-factorial, although the susceptible individual might result from the interaction of as few as three genes (Bailey *et al*, 1996). An international study, using affected first-degree relatives, has so far identified six potential sites, of which the most promising are on chromosomes 7q and 16p (International Molecular Genetic Study of Autism Consortium, 1998). Sufficient studies are under way to ensure replication of significant results – a welcome occurrence in a subject where isolated findings of uncertain significance have had a disproportionate impact.

Turner syndrome, with only one sex chromosome but derived from either parent, lends itself to a study of the effects of imprinting. A simple and elegant design has demonstrated marked impairment of sociability in those who get their X chromosome from their mother (Skuse *et al*, 1997), although the sex chromosomes have not otherwise been associated with autism. This implies the potential for localising the areas and systems relevant to sociability.

The opioid theory

The opioid theory proposes that autism arises from the early, long-term overload of the central nervous system by opioids, which are probably exogenous and possibly largely derived from incompletely digested dietary gluten and/or casein (Reichelt *et al*, 1991). Although difficult to substantiate, this theory draws together a number of disparate findings (Sahley & Panksepp, 1987). In essence, the theory is one of deficient barriers, the fault lying in the bowel mucosa, in the blood–brain barrier, or in the failure of the intestinal and circulating peptidases that should convert opioids to innocuous metabolites. The defective barrier may be either inherited or secondary to adversity. For example, a mucosal barrier might be affected by defective sulphation, the latter being an incidental finding in a study of dietary migraine (Alberti *et al*, 1999). Other therapists, blaming intestinal candidiasis, are using a combination of dietary and antifungal treatments.

More tangible has been the discovery of lymphoid hyperplasia near the ileo-caecal junction in children who had been selected on the basis of an autistic regression together with current bowel symptoms (Wakefield *et al*, 1998*c*). The regression occurred immediately after immunisation in only one-third of the subjects, but nearly all the biopsy specimens showed evidence of measles infection (Wakefield *et al*, 1998*a*). This suggests that measles might act in conjunction with another factor, whether genetic predisposition, intercurrent infection or multiple immunisation, to trigger a chronic inflammatory response. Another study by the same group implicates coincident mumps infection in the origin of inflammatory bowel disease (Montgomery *et al*, 1999). These results raise several issues that have become conflated. Is there a link between measles and autism, between measles and inflammatory bowel disease or between autism and inflammatory bowel disease? If so, are all autistic children vulnerable to measles infection or to the polyvalent nature of MMR? It would be helpful to know whether lymphoid hyperplasia occurs in the bowel of those who have had autism from birth or do not have bowel symptoms. Lymphoid hyperplasia is clearly distinct from Crohn's disease (Walker-Smith, 1998) and there is no evidence of the latter being associated with autism (Fombonne, 1998). Immediate post-immunisation gastrointestinal symptoms do not forecast autism (Peltola *et al*, 1998). In Gothenburg, a review of the 74 children diagnosed with autistic spectrum disorder over a 10-year period (Gillberg & Heijbel, 1998) included the introduction of MMR immunisation in 1982. If anything, they showed the incidence declined although this is not entirely consistent with their impression that the incidence of autism is increasing over time (Arvidsson *et al*, 1997). A study of the onset of autism in 498 cases in London did show an increase in prevalence, but showed neither the superimposed surge with the introduction of the polyvalent vaccine nor the temporal link with diagnosis that might be predicted (Taylor *et al*, 1999). Unfortunately, any conclusions are limited by the possibilities of changing diagnostic practice and catch-up polyvalent immunisation of those born earlier than the critical period.

While neither study (Gothenburg or London) can exclude the possibility that autism might be caused or triggered by polyvalent measles immunisation, they indicate that it does not account for more than a small proportion of cases. It will need a much larger study, with greater statistical power, to disprove a hypothesis that is already reducing MMR uptake and herd immunity.

A conbination of open case studies and media support has led to excitement about the effect of secretin, a pancreatic enzyme that triggers peptidase release. This interest is unlikely to be dimmed by the failure of five placebo-controlled trials to find a convincing response in their preliminary, unpublished presentations. However, the trials did identify the difficulties of measuring change in autism and the extent of natural fluctuation in its symptom patterns. Popular demand has led to the resumption of secretin production despite the lack of evidence of efficacy or safety in repeated dosage, let alone a treatment licence. Nevertheless, the reports invite a closer scrutiny of the role of the intestinal peptidases as well as of gastrin, the polypeptide upstream to secretin, which requires sulphation to become biologically active.

Dietary exclusion of gluten and casein has been incorporated into a number of approaches, even those that focus on child-rearing. Although there have been a number of positive reports about its effectiveness, systematic trials have come from only two centres, one working with children in a residential school (Knivsberg *et al*, 1998) and the other monitoring children living at home (Whiteley *et al*, 1999). The results are mixed, and insufficient to gauge how far success balances against partial or transient responses, a failure to respond, or natural remission. However, the evidence warrants further studies, especially placebo-controlled trials.

Naltrexone provides a pharmacological means of blocking opioid action. Its proponents describe a therapeutic U-shaped curve and emphasise that it is effective only in very low dosage (Scifo *et al*, 1991). It is therefore unsurprising that other, more definitive studies should fail to find anything other than modest and mixed effects at higher dosages (Campbell *et al*, 1993; Willemsen Swinkels *et al*, 1996; Kolmen *et al*, 1997). These studies leave naltrexone in an equivocal position, except for the general agreement that it does reduce hyperactivity – an important property in a condition where stimulants can increase stereotypy (Campbell *et al*, 1996).

There are many treatments for autism, each advocated with a zeal that undoubtedly

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makes for effectiveness. Unfortunately, such enthusiasm also makes it more difficult to evaluate how these treatments would perform in the hands of less charismatic practitioners. Most approaches depend on open, uncontrolled case reports and series that make little allowance for natural developmental change. The exception is the reporting of Lovaas's intensive behavioural technique (McEachin *et al*, 1993), although this too is under fire (Boyd, 1998; Gresham & MacMillan, 1998). Other home-based programmes are being shown to be effective (Ozonoff & Cathcart, 1998). Although some focus on one aspect of the child's deficit and can be applied without the need for the wholesale conversion of the family, most programmes demand the substantial sacrifice of time, attention and funds.

With inconsistent measures and differing populations it is difficult to make a coherent whole of a large number of observations. Cost-effective progress needs a greater coordination of efforts across a number of fields, using a variety of instruments and techniques, in order to get a multi-point fix – an approach that has been pursued by the Tours group for some years (Adrien *et al*, 1989). As in 19th-century exploration, well-mapped areas are outweighed by the unknown, from which emerge travellers' tales of strange practices and exotic cures.

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CLINICAL IMPLICATIONS

- Autism is a biological disorder that merits a medical approach in its management.
- As yet, there is insufficient evidence for the gluten- and casein-free diet to justify its routine use. There is still less evidence for the effectiveness and safety of secretin.
- The variability in the clinical course of autism makes it difficult to distinguish therapeutic response from natural fluctuation or remission.

LIMITATIONS

- This review covers only part of the field of autism research; it excludes, for example, developments in cognitive psychology.
- Autism is a clinical rather than a laboratory diagnosis. This means that research results may be based on a mixed population and reflect aspects other than autism.
- Measles, mumps and rubella (MMR) immunisation has been suggested as a factor in the development of autism. If so, it is a factor only in a small proportion of cases. This will make it difficult to demonstrate the safety of MMR.

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