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# The Emanuel Miller Memorial Lecture 1998
# Autism: Two-way Interplay between Research and Clinical Work

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The two-way interplay between research and clinical practice in relation to autism is reviewed with respect to: (1) diagnosis and syndrome delineation; (2) the nature of the disorder; (3) intervention studies; and (4) aetiology, as manifest during four time periods; (a) the 1950s and 1960s; (b) the 1970s into the mid 1980s; (c) the late 1980s and early 1990s; and (d) the late 1990s. It is concluded that clinical practice has changed out of all recognition during the last 50 years and that research findings have been crucial in bringing about that change. It has not, however, been a one-way traffic. Many key advances were prompted by astute clinical observations and some extravagant research claims were given a more balanced perspective through the light of clinical experience. Crucial research and clinical tasks remain but the means to meet them are there if the opportunities are taken and attention is paid to the lessons of the past.

*Keywords:* Autistic disorder, behaviour therapy, cognition, diagnosis, genetics, rating scales.

## Introduction

Research is the lifeblood of clinical practice in all fields of medicine, including child psychiatry (Rutter, 1998). It has become generally accepted that all of us, as clinicians, need to base what we do on solid empirical research findings. This is reflected, for example, in the growing ascendency of "evidence-based medicine". It is appropriate that we are challenged to demonstrate that we are using methods that work and that we are not neglecting approaches that are even more effective (Goodman, 1997). Nevertheless, there are dangers if we adopt too mechanical, and too simplistic, an interpretation of "evidence-based medicine". Of course, we need to know which treatments are most effective for which problems in which circumstances, and research has a crucial role to play in finding that out. Where, then, do the dangers lie?

Several points need to be made. First, the essence of research lies in the process of problem solving and not in the mere provision of a set of factual answers. Medawar (1982) brought this out well in his essays about the nature of scientific enquiry. A creative imagination is as fundamental as the rigorous testing of hypotheses. Research comprises the telling of stories about how mechanisms in nature might be operating, then using experimental-type strategies to test the ideas expressed in the stories, to compare alternative explanations, and gradually, in iterative fashion, to move progressively closer to what might be the truth. Second, as an extension of that same point, the most important thing is not to know which of our current methods are best but, rather, to have a means of moving forward to develop even better methods in the future. That can only happen if the research is devised to determine *why* methods work in particular circumstances and not just whether they are better than alternative approaches.

Third, major improvements in clinical practice are even more reliant on basic research into the nature of causal processes than on studies of treatment. By basic causal processes, of course, I mean not just the neural processes that underlie the workings of the mind, but also the psychological and social mechanisms that are crucial for the understanding of multifactorial disorders as they arise in social beings. Many of the greatest clinical advances have relied on research from the past that, at the time, seemed to have little clinical relevance (Dollery, 1978). Often, it takes many years to bring together findings that have arisen in disparate fields and to recognise how they may be employed for clinical benefit.

Fourth, it would be a mistake to portray the picture as a one-way traffic from research to clinical practice. The reality is more complex interplay, with each feeding into the other and each serving to correct the other's mistakes (Rutter, 1990), as will be illustrated by the story of autism considered here. Finally, it is necessary to appreciate that progress does not consist of a smooth consistent moving forward in which each step taken constitutes an improvement on what had been the situation before. Instead, it tends to proceed in a series of fits and starts with occasional false claims, mistaken inferences, and misleading enthusiasms taking the field in the wrong direction. That is as evident in research as it is in clinical practice. This need for research and clinical practice to move ahead together was clearly evident in Emanuel Miller's (1960, 1968) own writings on child psychiatry.

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In this paper I seek to illustrate the ongoing interplay between research and clinical practice by considering the disorder of autism. As we shall see, progress has often been possible only through the results of basic research far removed from child psychiatry. The reliance of genetic research on advances in molecular biology and the reliance of functional brain imaging on technological advances in physics constitute two obvious cases in point. In this paper, however, I will take these for granted, crucially important though they are, and stick to the research–clinical practice interface as it has operated in relation to studies of patients.

## The First Delineation of the Syndrome

The story starts with Kanner's delineation of the syndrome of autism in a seminal paper in 1943. The paper has rightly become a classic. It is quite remarkable how successful he was in identifying the key clinical features, and even in many of the inferences drawn from them. In an era that has sometimes been thought of representing "epidemic environmentalism", he was astute in suggesting that autism represented some kind of inbuilt deficit. A year later in 1944, there was a somewhat comparable independent account by Asperger (see Frith, 1991), but it did not make the same impact and it does not compare with Kanner's account in either incisiveness of observation or conceptual clarity.

The beginning, therefore, was provided by a set of clinical observations. In essence, Kanner was putting forward an hypothesis that autism represented a meaningfully distinctive disorder that differed from other psychiatric conditions and which might well prove to have a different aetiology, course, and response to treatment. The first question had to be whether Kanner's observations could be repeated in other patient samples. It took a little time for this to happen, but other confirmatory reports began to come in from many other centres. There was no doubt, therefore, that the pattern of behaviour described by Kanner did indeed exist and could be recognised by others.

The first research step with respect to syndrome definition, however, took longer. That is, it was necessary to undertake systematic studies to determine whether Kanner's hypothesis that the syndrome was meaningfully different from other psychiatric conditions could be confirmed. Three further research avenues (beyond syndrome delineation) that would have to be explored concerned the nature of the disorder, its aetiology, and response to interventions. In telling the story of the interplay between research and clinical practice in the period between 1943 and the present time, I shall organise the issues and findings in relation to those four themes, considering developments as they have taken place over four broad time periods: the 1950s and 1960s, the 1970s into the mid 80s, the late 80s and early 90s, and the late 90s[1].

[1] In placing areas of research within a particular time period, greater weight has been attached to when the research ideas and approaches first came to the fore than when papers were published, which was sometimes several years later.

Before turning to the research, a word is necessary on the clinical concepts as represented in Kanner's own writings, as well as in those of others. Like all of us, Kanner, remarkable clinician though he was, was a creature of his times, and inevitably his thinking was influenced by the zeitgeist within which he had to operate. Accordingly, during the late 1940s the clarity of Kanner's vision became eroded in some respects. Autism came to be viewed as an unusually early manifestation of schizophrenia, with its aetiology including the environmentally mediated effects of rearing by refrigerator parents (Kanner, 1949). It should be noted that these clinical assumptions were not based on research. Thus, there had been no attempt at that time to consider how one might test the notion that autism was part of schizophrenia. Similarly, there were no tests of the environmental causation hypothesis and, indeed, no consideration at all of the possibility that, insofar as the parents showed particularly personality characteristics, these might reflect genetic factors rather than environmental risks. Nevertheless, undeterred by the lack of research evidence, therapists were galloping down the road of interventions designed to ameliorate the supposed damage from adverse parenting (Bettelheim, 1967), a strategy widely perceived by families as blaming them for causing their children's problems (Rimland, 1965). Against that background, let me now turn to consider the first phase of the 1950s and 1960s, beginning with studies on diagnosis and syndrome definition.

## Phase 1: 1950s and 1960s

### *Diagnosis and Syndrome Delineation*

During this first time period, there were various attempts by committees, such as the Creak working party (1961), to produce lists of symptoms by which autism might be recognised (except by then it had come to be called "schizophrenic syndrome of childhood"). The first attempt to use empirical research findings to determine diagnostic criteria, however, came from the Maudsley Hospital study (Lockyer & Rutter, 1969, 1970; Rutter, 1966; Rutter, Greenfeld, & Lockyer, 1967). Children who had been diagnosed as suffering from autism (or rather "infantile psychosis", the synonym used at that time) were systematically compared with children attending the same clinic who received some other diagnosis and who were matched for age, sex, and IQ level (features all known to be associated with variations in symptomatology—see, e.g., Rutter, Tizard & Whitmore, 1970). Note the importance of having a comparison group with some other psychiatric disorder. The question was not how to differentiate autism from normality. The hospital porter could do that without skilled assistance. The relevant question was how to differentiate autism from other psychiatric disorders.

Using direct observations of the children, as well as systematic accounts from caregivers, the Maudsley Hospital study showed that there were only three domains of behaviour that were present in nearly all autistic children and that were significantly more frequent in the autistic group than the control group. These were: (1) a general

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failure to develop social relationships, together with various specific abnormalities in interpersonal functioning; (2) language retardation, with impaired comprehension, echolalia, and pronominal reversal; and (3) ritualistic and compulsive phenomena associated with repetitive stereotyped play patterns. A systematic follow-up into adolescence and early adult life, in which the children were seen personally, confirmed that these differences continued to differentiate the autistic group many years after clinic referral. These features, together with an onset before 30 months (as also emphasised by Kanner), were then taken as the defining characteristics of the syndrome.

So far, so good. However, the validation of diagnoses has to go beyond the features used to define the syndrome. It is necessary that validation test whether the syndrome differs from other conditions with respect to features other than symptomatology, such as aetiology, epidemiological characteristics, course of disorder, or response to treatment (Rutter, 1965). That first study provided preliminary evidence of that kind. The diagnosis of autism was associated with a distinctive pattern of scores on IQ tests, with persisting language delay and with poor employment prospects. In each of these respects, the autistic children differed significantly from their matched controls. Autism also differed from the general run of emotional and conduct disorders in terms of the high frequency with which epileptic fits developed in adolescence (Rutter, 1970). The clinical benefits that derived from this, and from other comparable studies, were both the availability of applicable diagnostic criteria and also the knowledge that the diagnosis carried clinical meaning and prognostic value.

## *Nature of the Disorder*

During this first phase of research, a greater understanding of the nature of autism has been derived primarily from three main types of research: follow-up studies, psychological studies, and comparative studies. Long-term follow-ups were undertaken of Kanner's cases (Eisenberg, 1956; Kanner, 1971; Kanner, Rodriguez, & Ashenden, 1972), Creak's cases (1963a, b), Lotter's cases (1974a, b, 1978), and children seen at the Maudsley Hospital (Rutter, 1970; Rutter et al., 1967). All showed considerable consistency in the broad pattern of behaviour from early childhood into adult life but, equally, all showed a remarkable heterogeneity in the degree of social impairment whenever outcome was assessed. Although the majority remain severely handicapped to an important degree, about one in six went on to obtain regular paid employment. Much the most important predictor of outcome was the children's initial level of nonverbal IQ. When this was in the severely retarded range, a good outcome was highly unlikely. The overall level of language impairment also proved to be quite important, especially at the top end of the range. Good social functioning in adult life, even in those without mental retardation, was unlikely if the child had not developed useful speech by the age of 5 years. The overall level of disturbance was of some slight prognostic importance but nonverbal IQ and language were far more influential.

Before these studies were undertaken, the general clinical view was that autistic children were not testable for IQ and language and also, that even if scores could be obtained, they carried little meaning because of the children's social impairment. The studies were influential in showing that both views were wrong. Given an appropriate choice of tests and administration by skilled and experienced clinical psychologists, the great majority of autistic children were testable. Moreover, the stability of their IQ scores over time was much the same as any other group of children and the scores were good predictors of clinical outcome. The findings made an impact on clinical practice in showing the importance of skilled psychological assessment and this came, over time, to be accepted as a necessary part of any diagnostic appraisal.

The follow-up studies were also crucially important in producing what was, at that time, an entirely unexpected finding. About a quarter of children with autism who had not shown neurological abnormalities when assessed in early childhood developed epilepsy during the follow-up period, with an onset most often during adolescence (Rutter, 1970). This finding did much to bring about a change of concept, from the view that autism was an acquired psychogenic disorder to a view that it might constitute a neurodevelopmental disorder based on organic brain dysfunction. This led clinicians to pay more attention to the possibility of an organic aetiology and it came to be accepted that an adequate clinical assessment had to include a systematic medical evaluation, together with the use of special tests where there were indications that they might be of value.

Psychological studies undertaken during the 1960s were informative in showing the very considerable extent to which autistic children's patterns of scores on cognitive tests were distinctive and unusual. Even on tests that did not involve any use of speech, autistic children performed badly when verbal or sequencing skills were required (Lockyer & Rutter, 1970). It was concluded that the problem was not lack of speech as such but rather a serious deficit in cognitive skills involving sequencing, abstraction, and other language-related functions. A series of well-planned, systematic experimental studies by Hermelin and O'Connor (1970) took things very much further in showing that autistic children made relatively little use of *meaning* in their memory and thought processes. Both sets of findings indicated that the social and behavioural abnormalities of autism might arise on the basis of a cognitive deficit that involved some aspect of abstraction, or conceptual inference. The further implication was that it might be desirable for treatment strategies to shift from insight-oriented psychotherapy to educational and behavioural approaches that sought to help children cope better with what might prove to be basic cognitive handicaps.

Comparative studies in the 1960s mainly focused on the differentiation from mental retardation (because autistic children had been shown to have low IQ scores) and schizophrenia (because of the severe abnormalities in relationships in both conditions and because of the supposition that autism might be an early manifestation

of schizophrenia). The experimental studies undertaken by Hermelin and O'Connor (1970) were decisive in showing the host of ways in which autistic children differed from well-matched groups of children with mental retardation but without the syndrome of autism. Kolvin (1971) and his colleagues in England, and Makita (1966) in Japan, both showed that the age of onset of psychoses in childhood followed a markedly bipolar pattern—with peaks under the age of 3 years and over the age of 11 years, with a very decided trough in between. The findings suggested a discontinuity between autism and schizophrenia, and Kolvin's (1971) systematic comparisons between the two groups showed many differences. In 1972, Rutter argued that the overarching generic concept of "childhood schizophrenia" should be abandoned. Autism and schizophrenia constituted disparate conditions requiring separate classification. It was also noted that there might be a possible third group of disintegrative disorders, involving a profound regression and behavioural disintegration after an initial period of apparently normal development—a clinical picture first described by Heller (1930) much earlier in the century, but one subjected to almost no systematic research. About this time, clinicians began to abandon the notion of autism as a psychosis, replacing it with the concept that it might constitute a neurodevelopmental disorder with the need, therefore, to approach treatment with developmental considerations in mind.

## *Intervention Studies*

During the 1960s, educational and behavioural approaches to the treatment of autistic children began to come to the fore. This was the time when the first special schools and classes for such children were established (Bartak & Rutter, 1971) through the initiatives of pioneer teachers such as Sibel Elgar (Elgar & Wing, 1969) with the support of parents and the establishment of self-help organisations such as the National Autistic Society, founded in 1962 (Wing, 1972) in the U.K., which brought together parents and professionals to work for a common cause. Parent groups stimulated, fostered, and supported the development of educational provision. During the 1960s there were the first reports of the application of operant learning principles to the modification of the behaviour of autistic children (Ferster & DeMyer, 1961; Lovaas, 1967). The positive side of these early reports was the demonstration that the experimental methods could be applied to the study of autistic children. They were also important in showing that careful functional analysis of children's behaviour and the appropriate use of reinforcement principles could lead to worthwhile changes in behaviour. Clinicians were, nevertheless, reluctant to move uncritically in the direction urged by these early behavioural enthusiasts. Four concerns predominated. First, behaviourists used their findings to argue that there was no need to postulate any kind of neurodevelopmental disorder, and this seemed to run counter to other evidence. Second, although the immediate changes in behaviour were striking, they had been brought about in rather artificial circumstances in the laboratory and the long-term gains in the natural environment remained unknown. Third, there was distaste over the use of punitive techniques, such as the employment of electric cattle prods in order to shape social behaviour (Lovaas, Schaeffer, & Simmons, 1965). Fourth, the use of material reinforcers (such as sweets or chocolates—Lovaas et al., 1966) seemed to carry the danger that children's behaviour would become reliant on artificial rewards.

As clinicians gained experience in the application of behavioural and educational approaches in the treatment of autistic children, the need for some modifications in treatment methods became apparent. Up to that time, it had been thought desirable to provide treatment on an inpatient basis because that enabled a higher intensity of therapeutic input. It soon became evident that, although behavioural methods did indeed result in symptomatic gains, the benefits tended to dissipate either on return home or on moving to a different setting within the residential facility (Lovaas, Koegel, Simmons, & Long, 1973). It was necessary to consider what steps should be taken to ensure that behavioural gains generalised. It was concluded that it was likely to be helpful to engage the participation of parents as co-therapists (Schopler et al., 1980, 1986) and to seek to introduce the educational and behavioural modifications in the children's natural environments of home and school. Various forms of community interventions were developed, including working with parents in their own homes (Rutter, 1973).

The other therapeutic shift arose in part from clinical experience and also in part from an appreciation that if autism constituted an abnormality of development (rather than a psychosis), it was important to plan treatment with developmental goals in mind and in the light of considerations of the principles of psychological development and of how autistic children's basic deficits might be impeding that development (Rutter & Sussenwein, 1971). Thus, there was a need to consider how to foster more normal social development, how to facilitate language development and communicative skills, and how to reduce abnormal stereotyped patterns of behaviour. It was decided that the clinical and cognitive research findings suggested that the social problem lay in autistic children's difficulties in engaging in social interaction rather than from their withdrawing from social encounters. Attention came to be paid to how to *intrude* on the child in order deliberately to engage him in interaction that was meaningful and pleasurable. Similarly, behavioural attempts to modify language came to focus more on communicative skills than on the acquisition of words as such. By the end of the 1960s, a quite radical change in the therapeutic approaches to autism was beginning to be established.

## *Aetiology*

This first phase included relatively little research into causes. However, there was the beginning of a series of reports that autism was sometimes associated with one or other of a mixed bag of medical conditions that had in common the presence of organic brain pathology. The 1971 study by Chess, Korn, and Fernandez of children

with congenital rubella provides a good example of just such a systematic study. At first, the importance seemed to lie in the sheer demonstration that autism might arise on the basis of some defined medical condition (and hence the implication that such conditions should be searched for). Questions also began to be asked on what these medical aetiologies might have in common and what brain mechanisms might underlie the development of autism. The answers, however, had to await a much later phase of research.

## Phase 2: The 1970s into the Mid 1980s

### *Diagnosis and Syndrome Delineation*

The second phase of the 1970s into the mid 1980s was associated with two main trends in diagnostic studies. As a degree of consensus on diagnosis came to be achieved, it was appreciated that it would be hugely advantageous for both research and clinical practice to develop standardised assessments (Parks, 1983). At first, a range of questionnaires were produced but, although they have their value, they did not prove to be satisfactory for individual diagnosis. Rather, it seemed preferable to develop standardised interviews and standardised methods of observation. Once more, various methods were tried (see Schopler & Mesibov, 1988), with Wing and Gould's (1978) Children's Handicaps, Behavior and Skills (HBS) schedule, and Schopler's Childhood Autism Rating Scale (CARS) leading the way (Schopler et al., 1980, 1986). But, over time, the Autism Diagnostic Interview (Le Couteur et al., 1989) and the Autism Diagnostic Observation Schedule (Lord et al., 1989) came to be the tools that were most widely adopted. The ADI, as the Autism Diagnostic Interview was to be called, provides an interesting bringing-together of clinical and research approaches. Clinical researchers who developed it were aware that although many of the problems associated with autism were severe, they were also quite subtle and specific in terms of the aspects of social reciprocity and communicative deviance that needed to be tapped. Accordingly, the interview was designed to obtain detailed descriptions of actual behaviour (rather than yes/no answers to structured questions) and behavioural codings made by the investigator on the basis of an operationalisation of diagnostic concepts. The interview is well standardised and has been shown to be reliable and have discriminative validity, but its style and qualities approximate closely to the ways in which most clinicians approach the task of differential diagnosis. The ADOS, as the Autism Diagnostic Observation Schedule came to be called, also had the particular quality of using a series of social tasks and situations in order to provide a "press" for social interactions. As with the ADI, although systematically standardised and operationalised, the style of observation required considerable clinical skills and appropriate training in the use of the observational tasks.

The second trend during the 1970s and early 1980s involved the growing appreciation of the heterogeneity of autism, together with the increasing awareness of the need to consider where to draw the boundaries of autism and how to differentiate it from other pervasive developmental disorders that seemed similar in many respects yet different in others. Five areas of inquiry warrant particular mention. First, Rett (1966) described a hitherto unrecognised syndrome in which girls plateaued or regressed in their early development, showing a loss of purposive movements, a failure of head growth, and social deficits that seemed somewhat autistic-like in their pattern. His initial paper did not get much recognition at first but when Hagberg and his colleagues (Hagberg, Aircardi, Dias, & Ramos, 1983) picked up the importance of the observation and reported a series of cases, Rett syndrome was rapidly put on the map. Some child psychiatrists emphasised the high frequency with which girls with Rett syndrome had been diagnosed as having autism (Witt-Engerström & Gillberg, 1987) but a more careful study of the children's behaviour indicated important differences (Olsson & Rett, 1987, 1990).

Second, there were numerous reports of autistic-like abnormalities shown by children with the newly recognised syndrome of the fragile X anomaly, an unusual form of chromosomal abnormality made manifest by culturing the chromosomes in folate-deficient media. As with Rett syndrome, however, more detailed studies showed that, although the anomaly could indeed be associated with the characteristic syndrome of autism (Hagerman, Jackson, Levitas, Rimland, & Braden, 1986), a particular form of social anxiety and turning away might be even more characteristic (Cohen, Vietze, Sudhalter, Jenkins, & Brown, 1989; P. H. Wolff, Gardener, Paccia, & Leppen, 1989).

Third, there were several reports of cases showing behavioural disintegration (Corbett, Harris, Taylor, & Trimble, 1977; Hill & Rosenbloom, 1986). In a few instances, this pattern was associated with some form of overt acquired brain disease, but in the great majority of cases, medical investigations proved negative. It remained uncertain whether this syndrome was an atypical variety of autism or rather something different (Kurita, Kita, & Miyake, 1992; Volkmar & Cohen, 1989). That question remains unanswered today.

Fourth, Wing and Gould's (1979) epidemiological study of mentally retarded individuals drew attention to the high frequency with which autistic-like syndromes occurred in children with profound mental retardation. Only some of these showed the classical syndrome as described by Kanner, but Wing argued that the syndromes nevertheless represented the same basic condition. The study was important in emphasising the several different ways in which the social deficits of autism might be manifest.

Fifth, there was a resurgence of interest in the concepts first proposed by Asperger and in the manifestations of autistic-like patterns in children of normal intelligence. Wing's (1981) espousal of Asperger syndrome and Wolff's (S. Wolff, 1995; S. Wolff & Chick, 1980) descriptions of what she at that time called schizoid disorder of childhood were particularly important in this connection. Questions were asked about whether these syndromes represented mild autism or some different condition.

Both clinicians and researchers therefore became aware of the need for careful systematic observation that went well beyond general statements about social impairment and social withdrawal. The importance of shrewd clinical

observation (as by Rett and Hagberg) were crucial in identification of the clinical heterogeneity although the subsequent research was necessary in order to validate it. The field had moved on dramatically from the undifferentiated concept of childhood schizophrenia.

During the second phase, attention turned to the nature of the language problems associated with autism. Research during the 1960s had made clear that it was not just that speech was slow to develop (or did not develop at all) but rather that the quality of language was abnormal and so was its communicative usage (Rutter, 1968). Was this, however, because the language deficit was so severe and pervasive in autism or was the nature of the language problem different in kind from that associated with developmental disorders of language? Bartak, Cantwell and others (Bartak, Rutter, & Cox, 1975, 1977; Cantwell, Baker, & Rutter, 1978; Cox, Rutter, Newman, & Bartak, 1975) sought to investigate this question by comparing boys of normal nonverbal intelligence with autism and boys with a similar cognitive level who showed a developmental disorder of receptive language. The findings showed that the language deficit in autistic children was indeed more severe and more extensive but the marked differences between the two groups could not be accounted for by the level of language. It was clear that autism involved a quite widespread cognitive deficit that included language but which extended much more broadly.

## *Aetiology*

The second phase of research saw many studies investigating different possible medical causes of autism (Coleman, 1976; Coleman & Gillberg, 1985; Golden, 1987). Several different strands with lessons for research and for clinical practice may be delineated. First, there were many reports that autism was associated with some medical condition. Almost all of these were based on single case reports or very small samples. The inferences to be drawn from these case reports were problematic for several reasons, as came to be recognised later. The findings were important, nevertheless, in highlighting the possibility that autism could arise on the basis of diagnosable medical conditions. These reaffirmed the need for a careful medical evaluation of all cases of autism.

The second strand is that more detailed studies of proven associations often showed that the autistic syndromes associated with medical conditions were atypical in one way or another. This was noted earlier in relation to Rett syndrome and the fragile X anomaly. The follow-up of the congenital rubella sample by Chess (1977) gave rise to the same message.

The final strand to mention is the evidence that genetic factors play an important part in autism. Earlier reviews had concluded that it was unlikely that there was a strong genetic influence because it was so rare for autistic individuals to be born to autistic parents and because the rate of autistic siblings was so low when considered in absolute terms (estimates at that time suggested it was about 2%—see Rutter, 1967). The situation changed when it was appreciated that these were not the relevant features. Follow-up studies had already shown how extremely rare it was for autistic individuals to marry and have children; accordingly, vertical transmission was not to be expected. Also, the point about the 2% rate was not that it was low in absolute terms but rather that it was so extremely high relative to the base rate of autism in the general population—estimated at that time at about 4 per 10,000. This led Folstein and Rutter (1977a, b) to undertake the first systematic twin study of autism. The sample was small but the findings were striking in pointing to the likelihood of a strong genetic liability and also in their indication that the liability probably extended beyond the traditional diagnosis of autism to include a broader range of social and communicative deficits in individuals of normal intelligence. Up to that time, most clinicians had tended to see autism as an extreme handicapping condition that was qualitatively distinct from variations within the normal range. Also, the general tendency within psychiatry was to view genetic factors as being likely to apply to the direct inheritance of disorders. Despite its slender empirical base (because of the small sample size), the study was one of the first to raise queries about both assumptions. It seemed that the genetically influenced liability to autism extended somewhat more broadly than had hitherto been appreciated and, also, it seemed that genetic factors might operate within a multifactorial context, rather than through Mendelian direct inheritance of discrete conditions.

## *Nature of the Disorder*

Following the lead provided by Hermelin and O'Connor, studies of the nature of autism during this time period continued to focus on gaining a better understanding of the nature of the cognitive deficits. The importance of low IQ as a predictor of outcome had been shown, but in itself that finding did not deal with the possibility that the low IQ scores might be secondary to social withdrawal. Several research programmes tackled this question. One research strategy was to determine, through naturalistic follow-ups, whether children's IQ scores varied with changes in their psychiatric state. Findings showed that they did not to any substantial extent (Rutter, 1979, 1983; Rutter et al., 1967). The second strategy was to test whether intensive educational and behavioural treatments led to significant IQ gains. The findings showed that they did not (Hemsley et al., 1978; Howlin & Rutter, 1987; Rutter & Bartak, 1973). A further strategy was to use a variety of tactics to examine the extent to which motivational factors might influence cognitive performance. Clark and Rutter (1977, 1979) found that autistic children's IQ scores were largely explicable in terms of cognitive factors, without the need to invoke motivation. Of course, motivational factors influenced the performance just as they did with any other group of children, but they did not account for the low IQ scores shown by many autistic individuals.

The conclusion was clear. Many autistic children had a general cognitive deficit that was not in any way secondary to social withdrawal. On the other hand, it was equally evident that low IQ in itself could not possibly account for autism. To begin with, a substantial minority of autistic children had a normal nonverbal intelligence and there were many markedly retarded children who did

not show autism. Where the low IQ was associated with a particular medical condition, the risk of autism seemed to vary according to the medical diagnosis, as shown by Wing and Gould (1979) amongst others. Thus, although Down syndrome and cerebral palsy occasionally co-occurred with autism, the association was much less strong than with, for example, tuberous sclerosis and infantile spasms (Hunt & Dennis, 1987; Riikonen & Amnell, 1981). The implication was that the specific nature of the underlying neuropathology might well be crucially important, although it was not at all apparent which aspects might predispose to autism. In addition, as already noted, the IQ scores of autistic children tended to show an unusual and distinctive pattern (DeMyer, 1975; DeMyer, Barton, & Norton, 1972; Lockyer & Rutter, 1970; Tymchuk, Simmons, & Neafsey, 1977). Although a general impairment in intelligence could well be important, there was also a need to search for more specific cognitive deficits.

In this search, researchers and clinicians had become increasingly aware of the need to focus on the possible ways in which a cognitive deficit might lead to the abnormalities in social reciprocity and social functioning more generally. Tinbergen and Tinbergen (1972) and Richer (1978) had hypothesised that autistic children were motivated to avoid social encounters but several studies showed that autistic individuals were most likely to respond socially when the social demands on them were increased (Clark & Rutter, 1981; McHale, Simeonsson, Marcus, & Olley, 1980). The findings provided no support for the motivational hypothesis and this view of autism began to fade away.

Over both of the first time periods, there was much research in which a range of physiological and psychological functions were examined in autistic children, their responses being compared with those of normal children. This led to claims that autism arose on the basis of perceptual inconstancy (Ornitz & Ritvo, 1968) or of a delay in sensorimotor integration (Ornitz, 1971) or of overselective attention (Lovaas, Koegel, & Schreibman, 1979). Many of the experiments were elegant and carefully designed. The problem was that there were no controls for mental age, and hence there was an inevitable uncertainty as to whether the findings were a function of low mental age or of autism. The need for appropriate controls was noted in an international symposium held in 1970 (Rutter, 1971), and this was underlined by DeMyer in 1975 and Yule in 1978. When the appropriate controls were introduced, as was the case in further studies of overselectivity (see Schover & Newsom, 1976), it became apparent that the level of cognitive impairment was more influential than the diagnosis of autism. Why it took so long for experienced researchers to accept the need for appropriate controls remains a bit of a mystery.

Two new approaches started to come to the fore in the 1980s. First, Hobson (1982, 1983, 1993) put forward the notion that autistic children might lack the ability to experience empathy and that this socioemotional deficit might constitute the key. The postulate fitted in well with clinical experience and his experimental studies confirmed the reality of the problems experienced by autistic children in differentiating emotions and some aspects of people.

The second approach focused on mentalising aspects of cognition, rather than emotions as such. Rutter (1983) reported a young adult with autism who complained that he "couldn't mind-read". The man explained that he thought that other people seemed to have a special sense by which they could read other peoples' thoughts and thereby anticipate their responses and feelings. By contrast, he was always upsetting people because he didn't realise he was doing or saying the wrong thing until *after* the other person became angry or upset. A breakthrough occurred with the development of experimental methods to test whether there was an understanding of other people's mental states. Wimmer and Perner (1983) devised experimental procedures based on tests of false belief. The paradigm involves a story in which the subject sees an article hidden in one place. Without the subject being aware, someone else then moves the object to an entirely different place. The test is provided by finding out whether the subject, in returning to reclaim the object, looks where the object actually is (which would require knowledge not available to them) or where they *think* it is. Given some form of portrayal of this story, children over the age of 4 years anticipated that the person would look where they *thought* the object was rather than where it *actually* was. Younger children, on the other hand, could not do that.

Baron-Cohen, Leslie, and Frith (1985) applied the false belief test to individuals with autism and showed that even older children with autism failed this test. It was postulated that the social impairments in autism might have arisen on the basis of this lack of appreciation of what other people might be thinking—something that came to be called a lack of a "theory of mind". What caught the imagination of the research world with this interesting finding was that, for the first time, it provided a possible means of directly linking a cognitive deficit with the social problem and that it did so in terms of an aspect of cognition known to follow a predictable developmental course. If confirmed, it was clear that this might well have major clinical implications.

### *Interventions*

The period of the 1970s and early 1980s was marked by a very widespread development of behavioural and educational approaches in the treatment of autistic children and by systematic investigations of their efficacy. At the beginning of the 1970s there were still claims that psychotherapeutic methods were better than educational approaches to the treatment of autism. Accordingly, Bartak and Rutter (1971, 1973; Rutter & Bartak, 1973) undertook systematic comparisons of a psychotherapeutic unit with little emphasis on teaching, a second unit in which regressive techniques and an emphasis on relationships were combined with special educational methods, and a third unit that provided a structured and organised setting with the focus on the teaching of specific skills. The results showed that clinical progress was greatest in the third unit—indicating the value of educational methods. The results were chastening, however, in their indication of the limited generalisation of the behavioural gains at school to the home environment, the continuing difficulties in understanding what they had

learned shown by many of the children, and the marked individual differences in outcome. The problem of generalisation was tackled by a range of programmes explicitly focused on working with parents in relation to the children's behaviour at home.

Schopler and his colleagues (Lansing & Schopler, 1978; Schopler & Reichler, 1971) established the TEACCH programme in which there was a behaviourally oriented curriculum, using parents as co-therapists, and with the details worked out on an individual basis, taking into account the child's developmental level and the parent's priorities and resources. Somewhat similarly, Hemsley, Howlin and their colleagues (Hemsley et al., 1978; Howlin et al., 1973; Howlin & Rutter, 1987; Rutter, 1985; Rutter & Sussenwein, 1971) developed a home-based treatment programme. A functional analysis of the children's behaviour was undertaken with the parents to determine when, where, how often, and for what apparent reason the behaviours occurred. Parents were helped to be consistent in their styles of interaction and handling and were advised to set aside *short* periods each day to teach the child specific social and communication skills, making the sessions as pleasurable as possible for both child and parents.

The research into the home-based treatment involved four main elements. First, systematic individual case studies were employed to determine whether the benefits demonstrated in laboratory or hospital settings could be replicated in the home, where there was much less control over the environment and with much more limited professional time. Second, it addressed the question of whether the treatment methods were *superior* to other approaches, examining longitudinal changes over a 6-month period. Third, the same 6-month comparison was used to determine the efficacy of the methods in altering parental behaviour. Fourth, the long-term benefits were assessed by means of an individually matched control group of children seen at the same clinic, but who lived too far away to be involved in the home-based approach, although the same principles were applied in giving the parents advice. The findings showed that the treatment programme brought about quite dramatic changes during the 6 months of intervention and that the long-term gains were both worthwhile and superior to those that followed other methods of treatment. On the other hand, the programme made no difference to the IQ levels and the gains in language development were quite modest. The main benefits were seen in relation to the behavioural problems and to overall social functioning. It was also noteworthy that there were huge individual differences in outcome, which were related in the same systematic fashion to the children's IQ and language as found in the earlier follow-up studies of children not treated in this way.

This same time period was marked also by the beginnings of a series of strong claims on the efficacy of treatment. Thus, the Nobel Laureate Tinbergen (Tinbergen & Tinbergen, 1983) stated boldly that: "it is becoming clear that many cases of autism can be cured and even prevented by a return to healthier forms of parenting" (p. 214). Similarly, Welch (1983) asserted that: "it is possible to restore an autistic child to normal development by establishing a secure mother–child bond" (p. 334). These various claims that autism could be cured proved controversial but, not surprisingly, they raised expectations among parents and professionals who wished to believe the optimistic message. Unfortunately, none of the claims were supported by controlled, comparative studies, and now, some 20 years later, such evidence has still to be obtained. The lesson is that we need to pay careful attention to the evidence put forward by researchers and not be overawed by their status or reputation.

Similar issues arose with respect to the unwarranted excitement over the claim (made rather prematurely on the basis of an uncontrolled study of just three children) that fenfluramine produced intellectual and behavioural gains in autistic children (Geller, Ritvo, Freeman, & Yuwiler, 1982). The reason why many people got carried away with the promise was because the benefits seemed to reflect what could be an underlying causal biochemical mechanism. It had long been appreciated that about a third of autistic children have raised serotonin levels in the blood (Cook, 1990), and one of the main effects of fenfluramine is to reduce serotonin levels. Many researchers were, nevertheless, sceptical because raised serotonin levels are found in many neuropsychiatric conditions (it is not in the least bit diagnosis-specific) and because there was no evidence in the published report that any benefits were systemically related to changes in serotonin level. The consequence was a mass of further studies with the much-needed controls. The findings showed that the benefits were modest indeed and such slight behavioural gains as occurred in some children were unrelated to changes in serotonin levels (Aman & Kern, 1989; Campbell, 1988). Looking back, it is doubtful whether, on the basis of such a slender and inadequate evidence, it was justifiable to spend so much money testing the benefits of fenfluramine. In the event, the drug has now been withdrawn from the market because of its possible toxic effects.

The claim was also made that high doses of the vitamin B6 led to worthwhile benefits in some autistic children (Rimland, 1987; Rimland, Callaway, & Dreyfuss, 1978). There was somewhat more substance to this claim, but the results were far from dramatic and, even now, there is uncertainty over the value of this form of treatment. Reviews of the evidence have usually resulted in the conclusion that the regular use of megavitamins is not justified (Sloman, 1991). However, that is to get ahead of the story of what was happening during the period of the 1970s into the mid 1980s.

## Phase 3: The Late 1980s and Early 1990s

### *Aetiology*

One of the most important products of the third phase of research during the late 1980s and early 1990s was consolidation of the quantitative genetic findings. Both a population-wide twin study in Scandinavia (Steffenberg et al., 1989) and a similar nationwide twin study in Britain (Bailey et al., 1995) showed a huge difference in the concordance rate for monozygotic and dizygotic pairs (60–90% vs. less than 5%). These figures translated into a heritability of the underlying liability to autism of about

90%, making it the most strongly genetically influenced of all multifactorial child psychiatric disorders. Because twins differ from singletons in various respects (for example, a higher level of obstetric complications), it is always necessary to check findings using other research strategies. Family studies of singletons were undertaken during this same time period by several different research groups in both Europe and North America (see Rutter, Bailey, Simonoff, & Pickles, 1997; Rutter, Silberg, O'Connor, & Simonoff, in press). The findings were consistent in showing a rate of autism in siblings of about 2–6%. This represents an increase in rate of some 60- to 100-fold as compared with the base rate of autism in the general population (Fombonne, 1998). The inference from this finding is the same as from the twin studies. At first, it had been thought that part of the increased risk might stem from obstetric complications but a more detailed examination of the evidence suggested that these did not account for the increased rate of autism in family members (Bolton et al., 1994, 1997).

Non-geneticists sometimes find it puzzling that researchers can conclude from the massive relative increase in risk for autism in the relatives of autistic individuals that genetic factors are powerfully influential, when the absolute rate of autism in relatives is so low. Initial estimates had put the rate in siblings at about 2% (Smalley, Asarnow, & Spence, 1988). The more thorough family studies showed this was probably an underestimate, with the true rate being more than 5%. Nevertheless, that still means that the great majority of siblings do not have autism. One of the main reasons for this apparent paradox is that several genes are involved. Pickles et al. (1995), using statistical modelling approaches applied to a combination of twin and family data, concluded that the findings suggested that autism was most unlikely to be due to a single gene but that, equally, more than 10 genes were unlikely. What this means is that many family members will have some of the genes that provide the susceptibility to autism, but they won't have all of them. In consequence, if combinations of genes are required in order for autism to develop, they will escape the handicapping condition.

The first twin study by Folstein and Rutter (1977a, b) had suggested that the genetically influenced liability to autism extended beyond the handicapping disorder. The twin and family studies undertaken during the late 1980s and early 1990s have confirmed that (Bailey, Le Couteur, Palferman, & Heavey, in press; Rutter et al., 1997; Rutter, Maughan, Pickles, & Simonoff, 1998; Szatmari, Jones, Zwaigenbaum, & Maclean, in press). The findings are persuasive that autism extends beyond the traditional handicapping disorder to include a broader range of social and communicative deficits in individuals of normal intelligence. This has come to be termed "the broader phenotype" of autism. What has proved much more difficult, however, has been the definition of the boundaries of this broader phenotype and, therefore, any determination of its frequency in relatives.

In essence, the relevant research strategies sought to tackle this question by determining not just whether there is an increased rate of some problem in relatives, but also whether its distribution in families was associated with other, better-established aspects of the broader phenotype and whether its distribution followed expected patterns and was not due to some other risk factor not representing a genetic liability. On this basis, it has been shown that mental retardation, isolated reading and spelling difficulties, and verbal deficits in cognitive functioning are almost certainly not indicators of autism unless they are accompanied by other autistic features—except possibly in the case of autism associated with profound retardation (Fombonne, Bolton, Prior, Jordan, & Rutter, 1997; Pickles et al., 1998; Starr, Kazak, Tomlins, Rutter, & Bailey, 1998).

DeLong and his colleagues (DeLong & Dwyer, 1988; DeLong & Nohria, 1994) noted an increased rate of affective disorders in the relatives of autistic individuals and it has seemed possible that depression or anxiety might, in some circumstances, constitute part of the broader phenotype. In the event, the lack of overlap with other features of the broader phenotype and the lack of an association with the severity of autism, but an association with affective disorder in other relatives, suggests that affective disturbance does not reflect a genetic liability to autism (Bolton, Pickles, Murphy, & Rutter, 1998). On the other hand, an increased rate of affective disorders in relatives seems to be a valid finding and its explanation remains obscure. The empirical evidence also does not support Gillberg's claim (1992) that eating disorders might be part of autism or the Comings' claim (Comings & Comings, 1991) that Tourette's syndrome might also be part of autism. Family studies have been consistent in confirming earlier findings that autism was not associated with an increased rate of schizophrenia in relatives. Follow-up studies (Volkmar & Cohen, 1991) have also confirmed that there was no increased likelihood, as compared with the general population, that autistic individuals would develop schizophrenia in adult life. It might well be expected that the broader phenotype would include obsessive-type features, highly circumscribed interests, and ritual or repetitive patterns of behaviour. Studies have indeed shown that such features are more common in the relatives of autistic individuals than in the relatives of controls, but the differences have been rather modest and so far it has not proved possible to derive good criteria to determine when such features are, and when they are not, part of the broader phenotype.

A lot of progress has been made in sorting out which characteristics define the broader phenotype, but many questions remain. So far, the evidence is compatible with a frequency of this broader phenotype in relatives of anything up to 20% or so and the findings do not, as yet, rule out the possibility that the liability is dimensionally distributed. That is, it always used to be assumed that you either had autism or you did not. That may still be the case, but the possibility that the autistic propensity operates as a continuum, with individuals varying as to how much or how little they have of autism, now needs to be reconsidered.

One clear clinical consequence of these quantitative genetic findings is that it has now become mandatory for clinicians to discuss with families the role of genetic factors in autism. The need for skilled genetic counselling is obvious. This is no straightforward matter because of the uncertainty over just how autism is inherited. It seems

unlikely that it is inherited directly. Several genes are almost certainly involved and there may be an interplay with as yet unidentified environmental risk factors. It is also apparent that the concept of the broader phenotype inevitably raises queries and anxieties in families in relation to the possibility that family members with social oddities or communicative problems may have a mild variety of autism. Clearly, this requires skilled handling. It has become necessary both for child psychiatrists to have a much greater understanding of genetics than has been the case in years gone by, and equally it has become critical for clinical and medical geneticists offering genetic counselling to have a much better understanding of the ways in which autism may present than will have been offered in their training in the past. The importance of genetic factors in multifactorial psychiatric disorders is no longer in doubt (Rutter, Silberg, et al., in press) but it is clear that there are challenges to both researchers and clinicians in the understanding of how genetic factors operate in these disorders and in developing sensitive and well-informed ways of handling the clinical implications.

The quantitative genetic findings just discussed all apply to autism when it arises in the absence of some associated, and possibly causal, medical condition. Over the same time period, there was a veritable flood of reports, mostly of isolated cases, of associations between autism and either some diagnosable medical condition or some somatic abnormality such as a chromosome anomaly (see Gillberg & Coleman, 1992). It has proved extremely difficult to know how to interpret these findings. They could represent nothing more interesting than coincidence. Thus, very few of the associations have been replicated. On the other hand, it is possible that some of the associations do reflect a valid connection and the challenge is to know which is which. It might have been hoped that the associations would give rise to a pattern that would provide clues on the nature of the underlying neural processes. Unfortunately, that has not proved to be the case either. Thus, when last reviewed, there were reports that autism was associated with anomalies in all but three chromosomes (Gillberg, in press). Similarly, autism has been associated with a mixed bag of metabolic abnormalities and with a range of infections in the prenatal period, and occasionally postnatally (Gillberg & Coleman, 1992). The supposed frequency of the association between autism and a diverse range of medical conditions was used by some to argue that autism was just an administrative category comprising nothing more than a set of nonspecific behavioural symptoms mirroring underlying brain dysfunction and, hence, that there was no point in searching for autism-specific causal factors (Coleman, 1990; Gillberg, 1992).

These arguments, although put forward by experienced researchers, were always unjustified and were regarded as such by other researchers at the time (see e.g. Rutter, 1991; Rutter & Schopler, 1992). The fallacy derived from several different considerations. First, the great majority of the associations were unreplicated and so their validity was not established. Second, the quantitative genetic findings suggested quite a high degree of specificity. Third, as already noted, it was not the case that all the medical causes of organic brain dysfunction greatly increased the likelihood of autism developing. The meaning of the differential associations according to the type of medical condition suggest that there may well be some commonality in the basis of different causes of autism even if the nature of that commonality is at present not known. Finally, the claim that 37% of cases of autism were associated with a diagnosable medical condition (Gillberg, 1992) seems likely to have been a substantial overestimate. Rutter et al. (Rutter, Bailey, Bolton, & Le Couteur, 1994), putting together the evidence from several studies, concluded that the rate was probably of the order of 10%.

Much the same story of inconsistent findings has applied to a wide range of biological investigations including brain imaging, metabolic studies, and neurophysiological investigations (Bailey, Phillips, & Rutter, 1996; Gillberg & Coleman, 1992). By sharp contrast, there has been a relatively high degree of consistency in the neuropsychological findings. It is clear that part of the problem in biological studies has lain in the lack of methodological rigour and a lack of concern that findings be replicated by other investigators under blind conditions. In addition, all too often there has been no attempt to determine whether the abnormalities are specific to autism or would be found in a range of other neurodevelopmental disorders. A further problem, however, is that investigators have often regarded an initial positive finding as providing a "minimum figure" (e.g. Gillberg & Wahlström, 1985), failing to appreciate the dangers of relying on findings based on small samples (Cohen, Cohen, & Brook, 1995; Pocock, 1983). The ratio of false positives to true positives in a small sample is necessarily much greater than in a large sample and the size of the difference between groups is no guide to the true strength of the association. The point is that, in order to achieve statistical significance, the difference in a small sample is bound to be a large one and the true difference will almost certainly be very much smaller. This crucial methodological point has been well demonstrated by Cohen and her colleagues (1995).

A further clinical implication drawn by some researchers was that a wide range of medical investigations, including lumbar puncture, EEG, brain imaging, and metabolic studies, should be undertaken as a routine (Elia et al., 1990; Federico et al., 1990; Gillberg, 1990a, b; Gillberg & Coleman, 1996). Most clinicians have resisted this invasive approach to medical investigation. The key question is how often the investigations lead to a diagnosis that cannot be obtained more straightforwardly through clinical history and examination. The answer is that it is rare for the tests to reveal undiagnosed medical conditions; many of the supposedly abnormal laboratory findings have no unambiguous clinical implications; and the clinical value seems so slight as not to justify the distress inevitably caused to young children if such investigations are routinely undertaken.

Despite the plethora of false dawns and misleading inferences, it would be wrong to dismiss all the biological findings during this decade of research as uninformative. To the contrary, considerably progress was made in clarifying the few associations that do appear to be valid and probably meaningful. First, there is good replicated evidence that tuberous sclerosis is associated with autism. Pooling studies, probably about 25% of individuals with

tuberous sclerosis show autism and nearly half show a pattern of behaviour that would meet the broader diagnostic criteria of a pervasive developmental disorder (Smalley, in press; Smalley, Tanguay, Smith, & Gutierrez, 1992). Considered the other way round, the frequency of tuberous sclerosis among individuals with autism is quite low, probably about 1–4%, but this represents a substantial increase over the base rate expectation. It is quite likely that this is particularly so when the autism is associated with epilepsy. It is easy to miss the signs of tuberous sclerosis unless they are specifically looked for and the clinical implication is that the medical examination should always seek to determine whether it might be present. The one chromosome anomaly that seems to be particularly associated with autism is a partial tetrasomy of chromosome 15 (Baker, Piven, Schwartz, & Patil, 1994; Cook, Lindgren, et al., 1997; Gillberg et al., 1991). The meaning of the association with other chromosome anomalies remains obscure but, given that they are not detectable clinically, routine karyotyping is probably desirable. The other chromosome anomaly that needs to be considered is the fragile X. The initial claims of a strong association with autism have not been borne out but, although the true rate of fragile X in autism is probably below 5% (Bailey et al., 1993), that is still high enough to warrant routine screening using DNA methods.

Strong claims had also been made for an association between a lack of development of the posterior cerebellar vermis and autism (Courchesne, Hesselink, Jernigan, & Yeung-Courchesne, 1987; Courchesne, Townsend, & Saitoh, 1994) but this has not been confirmed by other investigators (Bailey et al., 1996). It may be that cerebellar abnormalities are occasionally implicated in the causal processes leading to autism but it now seems implausible that a specific lesion in the cerebellum usually underlies the condition.

## *Diagnosis and Syndrome Delineation*

To a considerable extent, diagnostic research during this third phase was driven by genetic findings. Thus, an appreciation that the diagnosis extends more widely than originally envisaged has led to a focus on Asperger syndrome or mild autism occurring in individuals of normal intelligence (see, e.g., Happé et al., 1996; Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Ozonoff, Pennington, & Rogers, 1991; Ozonoff, Rogers, & Pennington, 1991). Because these milder varieties tend to be diagnosed much later (Howlin & Moore, 1997) there has also been an increasing interest in the diagnosis in adult life. Attention also turned to the other end of the age span, with studies focusing on the very early diagnosis of autism (Baron-Cohen, Tager-Flushberg, & Cohen, 1993; Cox et al., 1998; Lord, 1995). The standardised interview and observation measures were modified with an eye to making them more suitable for very young children and for older adolescents (DiLavore, Lord, & Rutter, 1995; Lord, Rutter, & DiLavore, 1998; Lord, Rutter, & Le Couteur, 1994; Lord, Storoschuk, Rutter, & Pickles, 1993). Home videos (Osterling & Dawson, 1994) and health visitor records (Johnson, Siddons, Frith, & Morton, 1992) were used to determine whether autism could be diagnosed when the children were very young; screening questionnaires (Dahlgren & Gillberg, 1989) were applied to general populations; and clinical studies (Gillberg et al., 1990) were undertaken to answer the same question. The findings showed that, although some children show recognisable features in the first year of life, in most cases it cannot be detected in a reliable and valid fashion until 18 months of age or thereabouts. Moreover, it is clear that the diagnosis is particularly difficult when mental retardation means that the child's mental age is below 18 months. The difficulties with respect to diagnosis in adult life, when autism has not been recognised earlier, are also considerable. In the absence of good information on developmental course during the preschool years, it can be quite difficult to sort out which problems in adult life are due to autism and which are due to some other sort of psychiatric problem. A decade earlier it had seemed that the diagnostic difficulties were becoming resolved but the extension of the diagnosis to a broader clinical picture emphasised that problems still remained to be tackled.

Both DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organisation, 1992) moved in the same direction in recognising the need to make provision for a range of autistic-like pervasive developmental disorders. There was explicit recognition at the time that the validity of these diagnostic differentiations within the broader group were unestablished in some cases and the need was for more systematic studies to examine the matter more closely. The provisional attempt to subdivide the disorders represented a step forward in the realisation that classification required systematic research if it was to move forward and that this required specification of the differentiations that required testing.

## *Nature of the Disorder*

This third phase of research involved an explosion of neuropsychological studies, initially focused primarily on the "theory of mind" findings but then broadening out to examine other significant functions. There can be no doubt that this has been a strong area of research. A range of ingeniously designed different tests employed by several independent research groups have made clear that there is indeed a strong association between an impaired ability to understand mental states and autism (Bailey et al., 1996; Baron-Cohen, 1995; Baron-Cohen et al., 1993; Frith, 1989; Happé, 1994a, b; Yirmiya, Erel, Shaked, & Solomonica-Levi, in press). Both the strength of the association and its relative (but not complete—Yirmiya et al., in press) diagnostic specificity strongly suggest that it is likely to be implicated in the cognitive basis of autism. Five main problems, however, remain to be resolved. First, if the cognitive deficit constituting the basis for autism (as postulated) is so narrow and highly specific, why is there such a strong association between autism and general mental retardation (Rutter & Bailey, 1993)? Second, if a deficit in "theory of mind" is responsible, and yet this does not ordinarily develop until the age of 3 or 4 years, why are the manifestations evident as early as 12 to 18 months? It could be that autism arises from

cognitive mechanisms that are precursors of the mentalising ability but, so far, it has not been possible unambiguously to demonstrate a causal relationship between a precursor and later theory of mind skills.

Third, the relationship between theory of mind skills and language have not yet been adequately sorted out. The two are associated (Happé, 1995; Yirmiya et al., in press) but the mechanisms involved have yet to be elucidated. Language impairments do not seem sufficient to account for failures on theory of mind tests because many autistic individuals with high verbal skills nevertheless fail the tests. On the other hand, the association is closer than originally envisaged. Fourth, some 20% of verbal children with autism pass theory of mind tests. It remains unclear whether they truly have theory of mind skills or whether they use alterative strategies to pass the tests.

Fifth, although it is not difficult to see how an impaired ability to understand other people's mental states might lead to the social and communicative deficits associated with autism, it is by no means so clear how it could give rise to the obsessive-like preoccupations and repetitive patterns of behaviour. It is also not evident how it could give rise to the unusual cognitive talents, or idiot-savant-like skills, found in a substantial minority of autistic individuals (Goode, Rutter, & Howlin, 1994). Psychological studies during the 1980s and early 1990s extended to include studies of executive planning (Ozonoff, 1994) and of central coherence (Frith, 1989; Frith & Happé, 1994). Empirical findings have shown that many individuals with autism have problems in planning and organisation, in using feedback, in switching to a new cognitive set, and in disengaging from perceptually salient stimuli (see Bailey et al., 1996). The findings fit in well with clinical observations but problems in executive planning have been found in a wide range of disorders and it remains uncertain whether there is a particular type of executive planning deficit that is more specifically associated with autism. Research into central coherence is at a much earlier stage but the evidence so far does suggest that individuals with autism have a tendency to process information in a piecemeal fashion rather than according to the overall "gestalt" or meaning. It seems possible that weak central coherence may play a role in the development of idiot-savant skills (Pring, Hermelin, & Heavey, 1995) and may predispose to repetitive behaviour patterns. However, that remains to be determined.

The neuropsychological findings undoubtedly carry the potential of providing a means to differentiate social deficits that are part of autism from those that are due to some other kind of problem. This is likely to be particularly important in studying the broader phenotype. That potential has, however, yet to be realised. Clinically, the findings have been crucially important in emphasising the role of cognitive deficits in socialisation and communication, and that has changed concepts of the meaning of the social deficit in autism. Hobson's research (Hobson, 1993) had been crucially important in forcing investigators to seek to understand its origins and in demonstrating that a difficulty in appreciating emotions was part of the problem. On the other hand, the overall pattern of evidence does not seem to support Hobson's notion that an emotional deficit is primary and accounts for the other features (Rutter & Bailey, 1993).

### *Intervention*

Intervention research during this decade provided a consolidation of what was known on the value of developmentally oriented behavioural and educational treatments (Howlin, 1998; Howlin & Rutter, 1987). However, the period was also marked by three areas of controversy. First, Lovaas and his colleagues (Lovaas, 1987; Lovaas, 1996; McEachin, Smith, & Lovaas, 1993) made strong claims that a very intensive (40 hours per week) home-based behavioural programme during the early preschool years can bring about normal functioning in some two fifths of autistic individuals; and that the findings were inconsistent with the view that autism was due to a neural abnormality. Critics have pointed to limitations in subject selection, research design, and most especially in the criteria used to conclude that the children were functioning normally (Gresham & MacMillan, 1998; Schopler, Short, & Mesibov, 1989). Clinicians have been concerned regarding the cost to families in emotional, financial, and practical terms if parents are expected to give up so much to concentrate on the autistic child. Also, the massive improvements that are supposed to follow the intensive treatment seem out of keeping with a broader range of evidence from other interventions (see, e.g., Sheinkopf & Siegel, 1998). What is clearly needed at this point is a systematic comparative study undertaken by independent investigators and that has yet to be done. Lovaas' findings can not be dismissed but, equally, they cannot be accepted as valid until there has been independent replication.

Second, there have been strong claims on the benefits of a range of specific therapies including auditory integration and facilitated communication. The latter term was applied to a variety of techniques in which autistic children were supposed to be helped to communicate through the role of a facilitator, who provided physical support to enable the children to point to letters or type or use some other mechanical means of expressing themselves. Quite a range of systematic studies have been undertaken to test these claims and the results have almost always shown that the responses are under the control of the facilitator rather than the autistic individual (see Bebko, Perry, & Bryson, 1996; Green, 1994; Rutter et al., 1998). Most of the other special interventions have not been adequately evaluated and uncertainty remains on their benefits. What is clear, however, is that the claims currently far outrun the empirical supporting evidence and it seems appropriate for clinicians to be sceptical about what can be achieved by these means.

Third, it has been argued that intervention programmes are much more effective if they can begin when the children are quite young—say, aged 2 to 4 years. It seems entirely reasonable that treatments should begin early and also it seems desirable to begin interventions before secondary problems develop. Nevertheless, although there is some indication that it pays to start treatment early (see Rogers, 1996), there is still a lack of good evidence on the extent to which really early treatments are more effective than similar methods that begin later. Even

so, given that there are no obvious advantages in postponing treatment, it seems reasonable to begin early, whilst at the same time undertaking studies to test the extent to which this makes a major difference.

## Phase IV: The Late 1990s

In turning now to the most recent phase of research, in the late 1990s, it is inevitable that it is rather too soon to assess the clinical implications and value of the research findings. Nevertheless, a brief survey of the research state of play may be useful in indicating the clinical advances to be anticipated.

### *Aetiology*

With respect to aetiology, probably the most exciting development is provided by molecular genetics. A combination of technological and conceptual advances has meant that it is now possible to localise susceptibility genes for psychiatric disorders and therefore, potentially, to identify the precise genes involved and to undertake the necessary research to determine their functional consequences (Plomin & Rutter, 1998; Rutter & Plomin, 1997; Rutter, Silberg, O'Connor, & Simonoff, in press). There is no doubt that this quest for susceptibility genes is likely to be successful over the next decade and that it will make a real difference to the power to determine the neural processes involved in the causation of autism. That should make it possible to devise more effective methods of prevention and intervention, although the extent to which this is possible, and the means by which it will happen, will be hugely dependent on the details of what is found out. In the meanwhile, given the unfortunate history of false positive findings in molecular psychiatric genetics in the past, there needs to be an appropriate combination of enthusiasm for the potential of this research and caution to avoid premature acceptance of positive findings before they are replicated.

Molecular genetic findings in autism got off to an unfortunate start with the claim of a positive finding in which a nonreplication followed within days. Cook, Courchesne, et al. (1997), using an association strategy, reported a connection between autism and the promoter region of the serotonin transport gene, but Klauck, Poustka, Benner, Lesch, and Poustka (1997) not only failed to replicate this finding but found the reverse (i.e. an excess of the long, rather than the short, variant). Most recently, the International Molecular Genetics Study of Autism Consortium (1998) reported the first positive lod score finding, using an affective sib-pair strategy, in relation to a location on chromosome 7. It remains to be seen whether this finding will hold up on replication in other samples by other groups. Whether or not it does, the existence of several large-scale molecular genetic studies in both North America and Europe (Maestrini, Marlow, Weeks, & Monaco, in press) means that replicated findings can certainly be anticipated to follow in the years to come. What will emerge, however, is not *the* gene for autism but rather several genes that, in combination, give rise to an increased vulnerability to autism. Such findings will revolutionise our ability to define the boundaries of autism and should open the way to understanding the basic neural processes involved. The much-needed integration of clinical, genetic, neuropsychological, and neurobiological perspectives in autism (Bailey et al., 1996) may at last be on the horizon, but the prospect is still some way off.

Although there had been earlier reports of postmortem studies (see, e.g., Darby, 1976) it is only during the 1990s that more systematic neuropathological studies have come to the fore. Kemper and Bauman reported findings on six cases in 1993 and Bailey et al. have similarly reported six cases in 1998. Several of the brains were of unusually large size and abnormalities were found both in the brain stem and in the cortex. The findings do not seem compatible with the notion that autism arises on the basis of some localised brain lesion. There is, nevertheless, still a difficulty in knowing how to interpret the findings. Do the abnormalities, for example, index the age when neural developmental went awry or do they index the parts of the brain involved in a system-wide malfunction? We do not know.

In his first paper in 1943, Kanner noted in passing that several of the children had unusually large heads. Recent clinical studies have confirmed this observation (Woodhouse et al., 1996) and it may be that this provides a clue to the nature of the neurodevelopmental abnormality. It remains to be determined, however, whether this characteristic is confined to individuals with autism or whether it is a feature that runs in families including both autistic and nonautistic members.

### *Diagnosis and Syndrome Delineation*

In many ways, the most striking recent findings on diagnostic patterns have concerned unexpected groups. Thus, Brown, Hobson, and Lee (1997) reported autistic-like patterns in children with congenital blindness and Rutter et al. (in press a) have done the same in children who had suffered profound privation in institutions in Romania prior to adoption by U.K. families. In both cases, although the children's behavioural patterns showed many similarities with "ordinary" autism, there were important atypicalities in both the details of the pattern and in its developmental course. The findings both emphasise the need for careful clinical attention to the details of children's social, communicative deficits and unusual repetitive behaviour patterns, and raise queries about the diverse ways in which these may develop.

The follow-up into adult life by Mawhood and her colleagues (Howlin, Mawhood, & Rutter, 1998; Mawhood, Howlin, & Rutter, 1998; Rutter, Mawhood, & Howlin, 1992) of boys with a severe developmental disorder of receptive language also showed a surprisingly high frequency of social deficits. The overall clinical picture was not that of autism but it was much closer to autism than had been the case when the boys were young. The findings raise once again the queries over the interconnections between autism and semantic-pragmatic language disorder (Bishop, 1989; Brook & Bowler, 1992; Eales, 1993).

Twin and family data (Le Couteur et al., 1996; Pickles et al., 1998) have also been used to examine the possibility that variations in symptom pattern may index genetic

heterogeneity. The findings so far have emphasised the huge variability in clinical pattern even when the genetic basis must be the same, as is the case within monozygotic pairs. Such pairs have been found to differ by more than 50 IQ points, for example. It is possible that there is a meaningful difference between autism that is associated with a lack of development of spoken language and other varieties (Pickles et al., 1998), and it may be, too, that the association with epilepsy (perhaps particularly when it develops during late adolescence and early adult life) may be a meaningful differentiator, although even those possibilities remain rather uncertain. The history of medical genetics (as well as the findings in autism showing associations with tuberous sclerosis or the fragile X anomaly) indicate that genetic heterogeneity must be expected but we have yet to determine quite how it can be recognised clinically.

### *Nature of the Disorder*

In the field of neuropsychological studies, the development that is likely to make most difference in the years to come is that provided by functional imaging (Rugg, 1997). It provides the means of determining which parts of the brain are active during particular cognitive tasks (Fletcher et al., 1995). Despite occasional assumptions to the contrary, it does not provide direct information on which parts of the brain are abnormal. What it does do, however, is provide a means of relating brain function and psychological performance. Thus, for example, it will provide a way of determining whether the minority of autistic individuals who pass theory of mind tests do so using the same part of the brain as that employed by normal individuals in dealing with tasks of this kind. It remains to be seen just what functional imaging findings will show but the method is likely to provide psychological studies with the means to span brain and mind in a way that has not been possible satisfactorily up to now.

### *Interventions*

There have been no major therapeutic advances in the last few years although there have certainly been worthwhile developments. For example, there has been increasing attention to the steps that may help adults with milder varieties of autism gain and hold down jobs, and become more socially independent (Mawhood & Howlin, 1998). Reviews of the findings on pharmacological treatments (Campbell, Schopler, Cueva, & Hallin, 1996; Lewis, 1996) have reaffirmed earlier conclusions that there is no drug that produces major behavioural improvements in most individuals with autism. There are several drugs that produce modest benefits in some children and their use for symptom reduction in selected cases is well justified. There is nothing equivalent, however, to the major improvements in schizophrenia brought about by appropriate neuroleptics or the value of tricyclics and serotonin uptake inhibitors in the treatment of depression. It is a puzzle because it might have been expected that neurotransmitters would be involved in the brain processes underlying autism and, hence, that one or other of the drugs affecting neurotransmitters should have been helpful. Nevertheless, at least so far, that has not proved to be the case. Whether or not genetic findings will open up more productive new avenues remains to be seen, but that is certainly a possibility.

## Conclusions

Clinical practice has changed out of all recognition in the last half century and research findings have been crucially important in bringing about those changes. It has not, however, been a one-way traffic. Many key advances were prompted by astute clinical observations and some extravagant research claims were given a more balanced perspective through their interpretation in the light of clinical experience. Many of the advances have come through clinicians and scientists working closely together and through clinician-scientists who combine skills and practice in both. Specialist research-oriented clinics have constituted an important development and are likely to continue to be so in the future. It has been crucially important, too, for researchers to be aware of the potential of advances in other areas of science and of the need to use new concepts and new technologies. The fields of genetics and functional imaging provide examples but so, too, do the contributions from experimental, developmental, and cognitive psychology. In many respects, academic psychologists transformed the study of autism at least as much as did clinician-scientists.

We may wonder what Emanuel Miller, were he alive today, would make of the transformation that has taken place in clinical practice with autism. Undoubtedly, he would be pleased at the ways in which interdisciplinary collaboration has been important in both research and clinical developments. Certainly, too, he would obtain great satisfaction from the ways in which research and practice, working together, have led to such worthwhile improvements in what can be done to help autistic individuals and their families, even though it remains a seriously handicapping disorder for which no cure is even remotely on the horizon. Nevertheless, he would, I think, be concerned to ensure that these advances feed through to community services and do not remain confined to tertiary care specialist centres. Doubtless, too, he would be relieved that some of the more mechanical, less humane, experimental treatments have not come to dominate clinical practice. I think he would be troubled by the extent to which evangelists among both researchers and clinicians have sometimes made excessive claims. Perhaps, too, he might be worried lest the market economy emphasis on destructive competition may foster such claims. However, I suspect that, most of all, he would be pleased at the ways in which careful attention to empirical research findings, and to their replication and testing out in the field, has enabled an avoidance of the worst excesses without too much proceeding down blind alleys. He would be delighted by the receptivity to new ideas and I imagine that he would look to the future with a mixture of great hope and enthusiasm combined with caution and concern to ensure both an appropriate depth of scientific understanding and a continued dedication to meeting the needs of patients and their families. Or am I

projecting my own views onto this important pioneer in the establishment of child psychiatry, as Emanuel Miller undoubtedly was? The research and clinical tasks ahead of us are even greater than those in which there has been progress over the last half century, but the means to meet them are there, provided the opportunities are taken and attention is paid to the lessons of the past.

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