FOREWORD

One of MRC’s roles is to review scientific fields to identify research opportunities and define the strategic approach to meeting important health needs. We have been pleased to undertake this review on the epidemiology and causes of autism for the Department of Health.

This report of the review is an important contribution to our understanding of what current research reveals about the occurrence and causes of autism spectrum disorders. It identifies gaps in knowledge about autism and we hope that our findings will stimulate the research community to develop proposals that address the key issues.

We recognised from the outset that there was expertise and opinion beyond the scientific community which needed to be incorporated to give the full picture. The way the review has been carried out has enabled this to happen. It is clear that the questions from the lay community played a crucial role in shaping the discussions during the review process and the balance of the report itself. We are grateful to the lay group for their energy and commitment to the process and for using their wider networks to bring the issues important to the wider autism community to the attention of the review. We intend to build on the experience we have gained through this partnership.

I want to also thank Professor Eve Johnstone, Chairman of the Review and all the members of the review groups. I especially acknowledge the contributions of the chairmen of the groups in steering their work. Dr Francesca Happé helped immeasurably in drawing together the individual scientific contributions to the report.

I hope this report will be useful not only to the Department of Health but also wider communities such as scientists, consumers and the general public. MRC’s aim for the future in autism research is to encourage scientific proposals for multi-disciplinary research around shared research strategies. We believe collaborations will lay the basis for more effective approaches to ameliorating the more disabling effects of autism spectrum disorders.

Professor Sir George Radda
Chief Executive
1. EXECUTIVE SUMMARY

Introduction

1. In March 2001 the Medical Research Council was commissioned by the Department of Health to provide it with a clear picture of what scientific research has revealed about the epidemiology and the causes of autism.

2. Public debate about autism research has focused on relatively few questions - almost exclusively on the suggested links between the combined measles, mumps and rubella (MMR) vaccination, bowel disorders and autism. This review considers broader questions relating to the causes of autism as well as the question of whether there has been a real increase in the more widely defined autism spectrum disorders (ASDs). The aim of the review is to consider the research evidence and to inform and clarify issues that would merit further research. Social care, education and organisation and delivery of services are outside the scope of the review.

Organisation of the Review

3. Three groups of scientists examined the research evidence and assessed the strength of the research-based knowledge in epidemiology and case definition, physiology and infection, psychology and behaviour.

4. Importantly, for the first time in an MRC research review, questions and other extensive input from lay people were incorporated from the outset. A Lay Group was set up comprising individuals from the autism lay community, including relevant charities, and the MRC Consumer Liaison Group. Members of the group put together a number of questions reflecting concerns put forward by parents and through the charities’ networks as well as some issues arising from letters sent directly to the MRC by members of the public. Two Lay Group members attended each of the scientific groups. All the questions have been addressed in this report (see Appendix 5).

5. Several meetings were organised between July and November 2001 to bring the four groups together. The final meeting included external expert opinion on the draft report to help ensure that it would attain a high standard of accuracy and balance.

Review Findings

What are Autism Spectrum Disorders?

Definition

6. Autism is defined by early signs of impairments in socialisation and communication and the presence of repetitive behaviours. The spectrum includes children and adults across the range of severity and intellectual ability, from severely impaired to high-functioning (termed ‘Asperger syndrome’). Approximately a third of children with autism appear to lose skills in their second year, but the significance, in terms of cause and life-course, is unclear.

7. Attempts have been made to define subtypes within the spectrum, but the significance of those that have been proposed is not yet clear.
Assessment and diagnosis

8. Recently, systematic assessment tools for history taking and observation have been developed, lessening the reliance on clinical judgement. These should allow clearer comparison across studies in the future. Diagnosis can be made at 2 or 3 years, by experienced practitioners, but may occur far later in children with very low or very high general ability.

Identifying individuals with Autism Spectrum Disorders in the general population

9. Identifying ASDs in the general population, rather than in individuals who have come to the clinic owing to specific concerns, raises its own set of particular challenges. To date, there is no screening instrument that would identify all and only those children with ASDs. Missing genuine difficulties, or raising unnecessary worries, are both serious problems. In addition, there are ethical concerns about diagnosing a child or adult about whom there has been no previous concerns.

How Common are Autism Spectrum Disorders and has there been an Increase?

10. Autism spectrum disorders affect many more people than has generally been recognised – approximately 60 per 10,000 children under 8. Methodological differences between studies, changes in diagnostic practice and public and professional awareness are likely causes of apparent increases in prevalence. Whether these factors are sufficient to account for increased numbers of identified individuals, or whether there has been a rise in actual numbers affected, is as yet unclear; although it is evident that significant numbers of people have ASDs as currently defined. The prevalence of autism in the adult population is not known.

What are the Main Causes of Autism Spectrum Disorders?

11. Most researchers believe that ASDs have a variety of causes. They could perhaps all affect the same brain systems, or they could impede development through disruption of the different abilities necessary for social and communicative development.

12. It is well established that there is a genetic component to ASDs, although it remains unclear how many genes may be involved. It is thought that several genes may be operating together to confer susceptibility. In a small proportion of cases, various single gene disorders and chromosomal abnormalities have been reported in individuals with ASDs. It is entirely plausible that the autism phenotype might be derived from a number of different genetic components. How environmental factors interact with genetic susceptibility is as yet unclear.

13. A variety of possible risk factors for ASDs have been suggested. The Lay Group questions focused on many of these including exposures, before or after birth to drugs, infections and heavy metals. In general, there is insufficient evidence to date to allow firm conclusions. Perinatal complications are thought more likely to be consequences rather than causes of a child’s ASD, and no specific prenatal exposures have been established as contributory. A small number of cases have been reported in which viral infection may have played a role. In relation to the combined MMR vaccine we conclude from our review that the current epidemiological evidence does not support the proposed link of MMR to ASDs. Our conclusions are consistent with the previous MRC Reviews and with the findings of other expert groups that have reviewed this question.
Physiological Abnormalities Proposed as Causes

14. There has been considerable recent interest in a number of suggested physiological abnormalities, affecting the gastro-intestinal tract, sulphation processes and the immune system. Casein and gluten free diets have been tried, with some reports of improvements, but there are to date no properly controlled studies described in peer-reviewed journals. Data are presently limited, and further research, including appropriate control groups, would be of value.

15. Since 1999, a small number of articles have reported there to be a specific gastrointestinal pathology for ASDs. Caution is needed in extrapolating these findings to ASDs more generally.

Suggested Physical Abnormalities

16. ASDs can co-occur with other conditions, but there is some debate as to the frequency of associated medical problems. Current evidence suggests many people with ASDs may have larger, heavier brains, with cellular abnormalities in a number of regions – but no large lesion has been found to be specific or universal in ASDs. Advances in functional brain imaging may improve understanding of the brain basis of ASDs. Studies to date have found under-activation in areas associated with planning and control of complex action, and in areas associated with processing socio-emotional information. Reports of neurotransmitter abnormalities have mostly either not been replicated or are inconsistent. The underlying basis of the observed association between ASDs and epilepsy needs clarification.

Suggested Psychological Abnormalities

17. It is important to know not only what is different in the brains and behaviour of people with ASDs, but also what is special about how they perceive and understand the world. There are three main psychological theories of ASDs at present, focusing on social understanding, control of behaviour, and detail-focus. The full significance of the proposed psychological differences has yet to be established. The implications for biological investigation and practical intervention have begun to be explored, particularly for social deficit theories. Further work to build bridges from theory to practice in this area is likely to be fruitful.

Factors that Influence the Severity and Course

18. Because ‘autism’ was first described in the 1940’s, little is currently known about later life course and old age in these individuals. People with autism spectrum disorders are at risk for psychiatric problems including depression and anxiety. To date, drug treatments act on symptoms of ASDs and not the core difficulties of social, communication and imagination functions.

Interventions

19. The terms of reference of our review did not include an assessment of interventions. This important topic is the subject of other recent reports or projects underway.
Taking Forward Research into Autism Spectrum Disorders

20. In considering the way forward for research on the autism spectrum disorders (ASDs), we have focused on the following strategic themes:

Researching and Refining Case Definition

21. Improved definition of the outward characteristics (phenotypes) of the subgroups within the spectrum, and overlaps with other conditions, will underpin research on causes and mechanisms. Accuracy and consistency of case definition and diagnosis is a crucial issue both for services and for research. Improvements will help researchers compare different studies with each other and across time. Further research is needed to develop and evaluate the tools for case definition.

Developing the Epidemiological Framework

22. Epidemiology has an obvious central role in addressing questions about prevalence, incidence and their relation to time, place and person within populations. In addition, an epidemiological framework is also essential to research on case definition, co-morbidity and natural history and as a basis for elucidating the contribution of environment and genetic influences.

23. A strength of recent epidemiological studies within the UK is their use of similar definitions and methods of ascertainment.

24. Considerable advances are being made internationally towards identifying candidate genes for autism spectrum disorders. New, large epidemiological studies that included genetic data would allow these advances to be taken forward fairly rapidly, in the context of a general population sample, to address questions about ‘environment’.

Enhancing Integrated Research Strategies

25. The UK has a 40 year history of internationally cutting edge research on autism spectrum disorders, particularly in developmental psychopathology, behavioural and molecular genetics, neuropathology and assessment. These basic science programmes provide a very strong platform on which to build an even more integrated, broad approach to defining risk factors and mechanisms, thus laying the basis for new and more effective approaches to diagnosis, treatment and perhaps prevention.

Developing Hypotheses about Abnormal Physiology

26. There are a wide range and variety of observations and theories on the suggested role of vaccines, drugs, toxins, infections and diet as risk factors for autism. Many of the studies of diet, intestinal permeability and inflammatory responses in the gastrointestinal mucosa have come from the UK and the field is relatively young and fragmented. Greater methodological rigour and independent replication are crucial in much of this work.

27. Many of the observations are interesting and in principle worth investigating. Moreover, potentially modifiable risk factors are attractive targets for interventions. A start might be made by
testing such hypotheses in robust but relatively simple research designs, so that the less likely ideas can be put to one side and further effort and investment can focus on the areas that strong preliminary evidence identifies as more likely to be productive.

**Strengthening Research Capacity and the Interface with Services**

28. Researchers, funders and service providers need to consider how best to achieve strategic, integrated research alliances both to sustain excellence and to develop new areas of enquiry; and to ensure the availability of sufficient and appropriately skilled manpower at the research-service interface.

**Adding Value Through Lay Participation**

29. The participation in this review of people with autism, carers and people with experience of patient support and advocacy groups has enriched both the process and outputs and represents an important milestone in autism research in the UK. Further partnerships are likely to be of benefit by providing researchers and funders with access to user perspectives, and lay organisations with access to scientific expertise.

**Taking the Next Steps**

30. There are several achievable steps that could be taken in near future to enhance services and research for autism spectrum disorders.

- Bring to the attention of policy makers in the UK health, social care and education departments, and to practitioners, researchers and lay audiences the results of the various national reviews relevant to autism spectrum disorders in a co-ordinated way to maximise the sharing of agendas and concerted actions.

- Consider whether specific initiatives are required to stimulate collaboration to further exploit UK strengths in the field and to address important questions where research is currently weak and could be strengthened.

- Encourage the research community to develop high quality research proposals for funding that address the key issues for research identified in this report.

- Build on the researcher–lay–funder partnership that was indispensable to this review. Extend it to ensure that the best evidence is easily available to all. Facilitate the growth of consumer involvement in the design, conduct and dissemination of research - as a means to enhancing its quality and relevance.
2. INTRODUCTION

What is Autism?

31. Autism is the name given to a set of neurodevelopmental disorders in which the way that a person communicates and interacts with other people is impaired. Kanner and Asperger first introduced the term “autism” for childhood disorders of social interaction over 60 years ago. Since then, our understanding of autism has changed profoundly. Wing and Gould introduced the notion of an autism spectrum, covering a range of ability levels and severities, but characterised by qualitative impairments in social, communicative and imaginative development. Today, autism is recognised as one of a number of related ‘pervasive developmental disorders’, which also includes ‘Asperger disorder’, pervasive developmental disorders-not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett’s disorder. This Review considers the full scope of the autism spectrum disorders (ASDs).

Advances in Autism Research

32. United Kingdom scientists have contributed significantly to the considerable research effort world-wide on increasing the understanding of the causes and epidemiology of ASDs. Significant advances over the last four decades include the following:

• The recognition that autism has a neurobiological basis, which manifests itself through behavioural abnormalities. The harmful notion of autism being “caused” by poor parenting has been completely refuted.

• Diagnosis of autism, or one of the other pervasive developmental disorders, can be made with greater certainty owing to the development of more accurate and sensitive diagnostic tools.

• The evidence that as yet unidentified genetic and environmental factors and their interplay play a key role in the triggering, development and outcomes of the ASDs — and that there is unlikely to be one sole cause.

• A much better understanding of the cognitive processes of individuals with ASDs and how they perceive the world, and application of that knowledge to developing rational intervention strategies.

• The application of brain imaging technologies to understanding structural and functional development in ASDs.

33. Notwithstanding these successes, many uncertainties and challenges for research remain. For instance:

• The causes of the various disorders remain, to a large extent, unidentified.

• There is no “cure” for autism, although there are some management strategies that seem to be effective for some individuals.

• People with autism also suffer from a number of physiological problems the significance of which — in terms of cause and development of ASDs — is unclear and sometimes controversial.
Rationale for the Review

34. Although autism research has made much progress, recent public debate has focused on relatively few questions - almost exclusively on the hypothesised links between the combined measles, mumps and rubella (MMR) vaccination of bowel disorders and autism. Because of the important public health implications of any such link, several expert groups and reports have considered these particular issues in detail\(^2\). While they acknowledge that there are interesting findings, they have found no persuasive evidence for such links. The broader question “What are the causes of autism?” therefore remains, as does the question of whether there has been a real increase - or are ASDs just being recognised and counted differently? It was in the light of these uncertainties that the Department of Health asked the Medical Research Council (MRC) to review research on the causes and epidemiology of autism.

Organisation of the Review

35. Expert scientific assessment was made of research strengths, gaps and opportunities. Lay participation was incorporated from the outset. The review subgroups were organised as follows:

- Epidemiology and Case Definition
- Psychology and Behaviour
- Physiology and Infections
- Lay Group

36. The Lay Group comprised individuals drawn from the autism lay community and the MRC Consumer Liaison Group (Appendix 1). The three topic oriented groups comprised scientists selected to ensure the range of required disciplines was included, and that there was a balance between those who had already worked on ASDs and those who brought an independent expertise; all also included observers from the Lay Group.

37. The Lay Group was responsible for identifying a number of questions for the Review to consider (full list at Appendix 5). These questions reflected concerns already put forward by parents to charities with members on the Group as well as some issues arising from letters sent directly to the MRC by members of the public. The questions were addressed either within the body of this report or were answered in Appendix 5.

38. Several meetings were organised that brought the four Groups together. The final meeting included external expert opinion on the draft report to help ensure that it would attain a high standard of accuracy and balance.

Perspectives and Balance

39. Lay and scientific perspectives converged on key issues of diagnosis and case definition, the need for research of the highest quality – relevant, published and available for independent scrutiny and replication.
40. The Review also facilitated the sharing of different perspectives. For instance, lay members emphasised that:

- many practical, everyday issues, such as the extent and management of bowel problems, have not been addressed by the established ASD research community

- parents, practitioners and the “grey literature” (non-peer reviewed reports) have a largely untapped wealth of knowledge to contribute

- research needs to play a greater role in informing parents about interventions, given that they are faced with a bewildering array of advice on interventions and claims for commercial treatments.

Scientists emphasised:

- the value of building on existing strengths in epidemiology, genetics, clinical and basic neurosciences and physiology, and on relatively large, methodologically rigorous, multidisciplinary programmes

- the lack in many areas of published, independently-replicated, systematic observations on which to build testable hypotheses.

Coverage

41. The assessment of the evidence and our comments on strengths, gaps and opportunities are based on a comprehensive and impartial reading of the available literature, including authoritative reviews where they existed. Inevitably, not all the evidence has been identified or evaluated and such omissions should not be taken to mean that the research questions or findings have no merit. We have given relatively more attention to a number of issues raised by the lay members and where the evidence is limited than to the very large body of literature in the established areas of research on the autism spectrum disorders.

42. The scientific members did examine some of the grey literature – conference reports, commercial information and observations from parents and practitioners – some of it as material on the internet. However, assessing these kinds of report was problematic. The reports were often inaccessible and most contained too little information to enable critical appraisal. By contrast, reports in the peer reviewed literature had generally been produced to standards that required conclusions to be supported by adequate data and enabled an assessment to be made of the methodological rigour.

43. Finally, and inevitably, new evidence will emerge even as this report is published, and new interpretations of existing research will be made. Our account of the research and the final section on “the way forward” should be viewed with that caveat in mind.
3. WHAT ARE AUTISM SPECTRUM DISORDERS?

44. Autism Spectrum Disorders (ASDs) are diagnosed on the basis of qualitative abnormalities in social, communicative and imaginative behaviours, and the presence of repetitive and stereotyped patterns of interests and activities. Diagnosis is complicated by the varied manifestation of these core deficits, by wide variation in ability level, and by developmental changes. There is considerable heterogeneity, and subgroups might be usefully distinguished. There are now systematic tools for diagnosis, through parental interview and direct observation – and these should allow greater comparability of research samples across studies in the future. Population-based screening for ASDs is complicated by the need to check negative findings, and ethical issues in identifying undiagnosed individuals at the high-ability end of the autism spectrum.

Defining Autism Spectrum Disorders

45. In the absence of a specific biological marker (e.g. blood test) for ASDs, ‘autistic disorder’ is defined by behavioural criteria. These criteria have evolved over the almost 60 years since Kanner and Asperger first introduced the term autism for childhood disorders of social interaction. In response to research findings, there has been a progressive widening of diagnostic criteria. Kanner and Eisenberg identified as the two key features of autism, social aloofness and insistence on sameness, and to these Rutter added impairment in language development. Wing and Gould introduced the notion of an autism spectrum, covering a range of ability levels and severities, but characterised by qualitative impairments in social, communicative and imaginative development. It is this ‘triad’ of impairments that is captured in current international classification systems (the World Health Organisation’s “International Classification of Diseases”, 10th edition (ICD-10), and the American Psychiatric Association’s “Diagnostic and Statistical Manual,” 4th edition (DSM-IV). These reflect agreement in the field that ASDs are characterised by early emerging (before 3 years old), qualitative (i.e. abnormal and not merely delayed development) impairments in social interaction, communication (and imagination), with restricted and repetitive interests and activities (see discussion of diagnostic systems in Gillberg and Coleman).

DIAGNOSTIC CRITERIA FOR CHILDHOOD AUTISM
International Classification of Diseases (ICD-10) issued by WHO 1993

A Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas:
(1) receptive or expressive language as used in social communication;
(2) the development of selective social attachments or of reciprocal social interaction;
(3) functional or symbolic play.

B A total of at least six symptoms from (1), (2) and (3) must be present, with at least two from (1) and at least one from each of (2) and (3):
(1) Qualitative abnormalities in reciprocal social interaction are manifest in at least two of the following areas:
(a) failure adequately to use eye-to-eye gaze, facial expression, body posture, and gesture to regulate social interaction;
(b) failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities, and emotions;
(c) lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people’s emotions; or lack of modulation of behaviour according to social context; or a weak integration of social, emotional, and communicative behaviours;
(d) lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. a lack of showing, bringing, or pointing out to other people objects of interest to the individual).
The core difficulties in ASDs are manifest in different ways, according to age and developmental level.

(2) Qualitative abnormalities in communication are manifest in at least one of the following areas:
(a) a delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime as an alternative mode of communication (often preceded by a lack of communicative babbling);
(b) relative failure to initiate or sustain conversational interchange (at whatever level of language skills is present), in which there is reciprocal responsiveness to the communications of the other person;
(c) stereotyped and repetitive use of language or idiosyncratic use of words or phrases;
(d) lack of varied spontaneous make-believe or (when young) social imitative play.

(3) Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities are manifest in at least one of the following areas:
(a) an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus;
(b) apparently compulsive adherence to specific, non-functional routines or rituals;
(c) stereotyped and repetitious motor mannerisms that involve either hand or finger flapping or twisting, or complex whole body movements;
(d) preoccupations with part-objects or non-functional elements of play materials (such as their odour, the feel of their surface, or the noise or vibration that they generate).

C. The clinical picture is not attributable to the other varieties of pervasive developmental disorder

46. Throughout this review, the term Autism Spectrum Disorders (ASDs) is used. The notion of a spectrum of autistic disorders is reflected in the inclusion of ASDs among ‘pervasive developmental disorders’ in DSM-IV and ICD-10, which also includes ‘Asperger disorder’ (currently distinguished from autistic disorder by absence of significant language delay, and general intellectual skills in the normal range), pervasive developmental disorders—not otherwise specified (PDD-NOS), disintegrative disorder, and Rett’s disorder. This last disorder, although showing similarities with ASDs in its early stages, shows characteristic progressive physical regression, and is not currently conceptualised as part of the autism spectrum (and as such is not reviewed here). Although the diagnostic criteria for autistic disorders are well agreed, those for other subgroups are more controversial – and those for Asperger disorder, in particular, have been debated in the literature.

47. Diagnosis is complicated by the range of manifestations of each of the triad of impairments. Thus an individual may show qualitative impairment of social interaction in the form of aloof and indifferent response to others, passivity, or over-friendly ‘active-but-odd’ behaviour. Communication impairments, too, may vary from complete muteness to over-literal and pedantic, but verbally fluent and erudite, language. People with ASDs, in a similar way to people without, show individual differences as a function of personality, family and social environment, educational and vocational opportunities, and so forth. Also contributing to the challenge of diagnosis is the change in manifestation with age – autism, even in the same individual, may look very different at 5 and at 15 years of age. For example, lack of pretend play is a striking manifestation of the imagination impairment in childhood, but in adulthood the same impairment is often seen instead in lack of interest in fiction, and fascination with facts (e.g. memorising dates or timetables). It is clear that ASDs persist and that children with ASD become adults with ASD, with their own complex needs. The course of development into old age is as yet unknown, and further research is needed.
In terms of behaviour, ASDs may lie on a continuum with typical development, but they may prove to be distinct in biology, psychology, or in terms of clinical need.

48. The answer to this question may depend on the level of explanation considered: behavioural, psychological or biological. For example, at the biological level, we do not know whether the genetic or other causes of ASDs represent extremes of factors found throughout the rest of the population. Regardless of whether the biological cause is qualitatively or merely quantitatively distinct in ASDs, it may still be considered a clinical condition on the basis of the adverse consequences at the behavioural level. A parallel may apply with, for example, high blood pressure, where normal variation and clinical condition lie on one continuum. Although some individuals have extremely high blood pressure (‘malignant hypertension’), for the majority of the population the issue is where the cut-off lies that defines normality/abnormality, in relation to adverse future outcome. Lastly, even if the biological causes and behavioural features lie on a continuum fading smoothly into ‘normality’, it would still be possible that ASDs are distinct at the psychological level: people on the autism spectrum may be qualitatively different in how they perceive and understand the world – as some high-functioning individuals with an ASD have suggested in their autobiographical accounts.

49. At a practical level, the distinction between an ASD and ‘normal eccentricity’ is determined by clinical need; while one person with Asperger syndrome may find a niche and manage well without ever receiving a diagnosis, many others will come to clinical attention (sometimes in adulthood) because of social difficulties and associated mental health problems (e.g. depression). Diagnosis in these cases aids understanding of strengths and weakness and ends mistaken blame, for both the individual him or herself and family members.

Can we define subgroups within ASDs?

50. The notion of a unified spectrum, across severity and ability levels, is supported strongly by genetic evidence (co-occurrence in the same families) and, to a lesser extent, by clinical reports of developmental change (e.g. a child with ‘classic autism’ may develop into a teenager with characteristics resembling the Asperger picture). However, the clear heterogeneity within the spectrum has also led researchers to look for subgroups. In principle, subgroups could be formed at several different levels of explanation (biological, cognitive, behavioural levels). Groups defined by, say, genetic characteristics, may not, however, map onto groups defined by behavioural characteristics or educational difficulties. Clearly, the relevance of any subgroups will depend on the purposes for which (biological, psychological, or behavioural) similarities and differences between people with ASDs are being noted.
To date most attempts to define subgroups have been at the behavioural level. The diagnostic manuals (DSM-IV, ICD-10) identify various subtypes, three of which are currently considered part of the autism spectrum (autistic disorder, Asperger syndrome, and atypical autism or ‘Pervasive Developmental Disorder - not otherwise specified’ (PDD-NOS; see Gillberg & Coleman14 for discussion). Other attempts to define subtypes include 1) Wing’s passive, aloof, active but odd1; 2) low, medium and high-functioning15, 3) non-regressive and regressive subtypes differentiated by age of onset. At present, none of the proposed subdivisions of ASDs have been validated at the cognitive, neurobiological, or aetiological level. The distinction between high-functioning autism and Asperger syndrome, currently made on the basis of language delay in the former only, is contentious; groups so defined seem far more alike than different when examined in adolescence17. 

It is important to note, also, that because ASDs are pre-eminently developmental disorders, an individual may fit one subgrouping at one stage of development and another at a later developmental stage. Behaviourally defined subgroups therefore do not, at least as yet, appear to relate to aetiology or prognosis. However, behaviourally defined subtypes have practical usefulness (at least as short-hand descriptions of abilities and needs) and may be helpful for individuals with ASDs, parents and service providers.

Can regressive autism be considered a separate subtype of autism?

In between 15-40% of children with ASDs, seemingly normal development for 15-19 months is followed by loss of vocabulary, a reduction in social interaction and responsiveness, and sometimes an increase in repetitive play behaviour18,19. The level of vocabulary knowledge reached before the loss is often small (usually less than ten words). The reason for apparent regression of this type is unknown, and it is as yet unclear whether regression marks out a subgroup with a different aetiology or prognosis20. To date few differences have been found between those children who showed loss of spoken words and those who did not, when considering the clinical picture in later childhood21. However, data on this question are limited. In particular, we do not know whether loss of some early words is a more widely experienced phenomenon among the general population, and whether this has any prognostic relevance.

In a few rare cases, development is normal for at least two years, followed by a devastating regression in several areas of functioning before the age of ten. In such cases the diagnosis of Childhood Disintegrative Disorder may be made. Loss of social and communicative skills may also occur later in life (adolescence/early adulthood), in very rare cases, following an illness such as viral encephalitis22,23. Rett's syndrome is marked by severe physical and mental regression, with some autism-like features, and is considered a separate diagnostic entity, not considered further in this review.

More recently, there has been great interest in an acquired aphasia (language impairment) with epilepsy (Landau-Kleffner syndrome24) and electrical status epilepticus during slow wave sleep (ESES). These disorders are poorly understood. The children are described as having normal early development followed by a subsequent loss of speech accompanied by sub-clinical epilepsy and a characteristic underlying EEG abnormality. This characteristic abnormal EEG pattern is only seen when a sleep EEG is undertaken.

Approximately a third of children with autism appear to lose skills in their second year, but the significance, in terms of cause and life-course, is unclear.

ASDs are very varied and it may prove useful to distinguish subgroups, at least for shorthand description of similar strengths and weaknesses – however, we do not yet know whether groups with different behaviour have different biological causes or long-term outcome.
Assessment and Diagnosis in the Clinic

55. Systematic assessment tools have been developed in recent years, lessening the reliance on clinical judgement, which was up until now the only gold standard. History taking and direct observation have different strengths and weaknesses, and are best used in combination – although it is unclear how to balance these sources of information if they conflict. The new assessment tools allow clinicians to measure degree of impairment, as well as deciding whether an individual passes a threshold for diagnosis. Use of these instruments in the future should ensure that different research studies are including comparable groups of people with ASDs.

56. Even in the presence of agreed broad diagnostic criteria for ASDs, the methods by which information has been obtained when a child or adult comes to the clinic have varied. In the past, parental interview and direct observation have been unstandardised, with clinical judgement (of what constitutes, for example, qualitative impairment in social interaction, given a child’s age and intellectual level) remaining crucial. More recently, complex diagnostic instruments have been developed, to allow systematic collection of developmental data relevant to diagnosis. Examples of such instruments are the Autism Diagnostic Interview – Revised (ADI-R), the Autism Diagnostic Observational Schedule (ADOS-G), and the Diagnostic Interview for Social and Communication disorders (DISCO). These instruments are to be administered by interviewers who have good knowledge and understanding of the features of autism spectrum disorders (in part, based on direct observation of the clinical manifestations) and additional specific training in the use of these instruments.

57. Interview and observational approaches have distinct advantages and disadvantages; retrospective reporting may be hard for parents of older offspring, while brief observations in clinical settings may miss key features. The most satisfactory approach would appear to be to combine interview and observational measures. The diagnostic instruments provide data for use in diagnostic algorithms that generate ICD-10 & DSM-IV diagnoses. Even so, following assessment using these instruments there may still be diagnostic uncertainty that can only be resolved by expert clinical opinion following review of clinical information. The uncertainty stems partly from the fact that the algorithms are not well developed for diagnosing the full autism spectrum, partly from the lack of well established procedures for combining information from different sources (e.g. interview and observational assessment) when inconsistent, and partly because the diagnostic significance of different behaviours varies according to overall level of functioning.

58. Further difficulties arise because by their very nature developmental disorders change with age and in relation to the use of these instruments in very young children, older adolescents and individuals with severe intellectual impairment. That is because in the very young or developmentally delayed individuals the limited range and repertoire of social communicative behaviours makes it difficult to determine whether the qualitative abnormalities that characterise ASDs are present. In older individuals, changes in the person’s behaviour coupled with the problems parents have in recalling early developmental details may result in doubts about diagnosis.
Notwithstanding the challenges and complexities, discussed above, significant improvements in the assessment of ASDs have been made over the last 10 to 15 years. The detailed assessment tools now available show high levels of reliability and validity. In addition, the tendency has been in recent years for expert groups to share the same assessment paradigms across studies, which allows for more direct comparison of groups of people with ASDs than was previously possible. Finally, these diagnostic assessment tools have incorporated the conceptual changes that have occurred in the last 20 years, and reflect the current view of ASDs as a spectrum. They therefore provide data that can be treated both as continuous scores (reflecting degree of impairment in one or more areas) and as categorical information (meeting or not meeting clinical criteria for ASDs). The systematic use of these comprehensive standardised tools to collect detailed developmental data should allow investigators to remain free of the premature assumptions and frequent changes that may be made in various diagnostic systems. Rather, collecting systematic, reliable data at the symptom level should allow investigators to subsequently apply to their data changing or competing diagnostic algorithms, thus allowing more systematic test of their properties and more meaningful comparison of subjects across samples. This trend is, however, fairly recent and the implication is that most of the existing literature, and especially that dating back more than 10 years or so, is plagued by the lack of comparability in assessment procedures used by different investigators.

How early can you diagnose ASDs?

There are a number of studies reporting that the majority of parents are aware that something is not quite right in the months leading up to the second birthday. In a study of individuals aged 2 to over 40 years, the average age at diagnosis was 5 years for autism and 11 years for Asperger disorder. Age at diagnosis is likely, however, to vary greatly by region (according to services available), by year (with age at diagnosis falling in many places), and by the nature of the ASD (with high-functioning, and perhaps severely intellectually impaired, people being diagnosed later).

The American Academy of Neurology and the Child Neurology Society published practice parameters for the screening and diagnosis of ASDs. The published guidelines not only recommend early screening and access to diagnosis, but also make it mandatory for clinicians to make referrals to appropriate early intervention programmes. Such recommendations emphasise the importance of minimising the time delay between recognition of symptoms/difficulties, referral for diagnosis and in turn access to early intervention resources. In the UK, it is hoped that the effect of a current working group will be to facilitate the development of working guidelines and protocols for timely diagnosis, and the early intervention for pre-school and school-aged children. The National Initiative on Autism: Screening and Assessment (NIASA) has been set up by the Royal College of Paediatrics and Child Health and the Faculty of Child and Adolescent Psychiatry, Royal College of Psychiatrists with the support of the National Autistic Society (NAS) and the All-Party Parliamentary Group on Autism (APPGA). It is hoped that the working group will, over the next 12 months or so, facilitate the development of working guidelines and protocols for timely diagnosis and early intervention of ASDs in pre-school and school aged children.
Identifying individuals with autism spectrum disorders in the general population

62. Identifying autism spectrum disorders among the general population, rather than in individuals who have come to the clinic due to specific concerns, raises particular challenges. To date, there is no screening instrument that would identify all and only those children with autism spectrum disorders. Missing genuine difficulties, or raising unnecessary worries, are both serious problems. In addition, there are ethical questions about diagnosing a child or adult about whom there has been no previous concerns.

63. When ASDs were considered rare and severe disorders, finding individuals with ASDs through clinical or educational records (so-called ‘passive’ case ascertainment) was considered sufficient, on the assumption that they were likely to have come to clinical attention. With the realisation that ASDs include a spectrum of manifestations, including subtle signs in people of normal or high intelligence, the need for more active and systematic methods of case ascertainment for research has become clear (so-called ‘active’ case ascertainment). As a result, epidemiological studies have attempted to adopt more thorough procedures for case identification. In such population-based studies, completeness as well as method of ascertainment is important. Studies that rely on records of health service use, special educational needs and so on, are likely to produce biased estimates of frequency and associated factors. Population-based studies which use a two-stage process, comprising an initial test to actively ascertain potential cases and a subsequent diagnostic interview of those potential cases to confirm diagnosis and collect detailed information, are likely to be more valid. However the completeness of ascertainment (i.e. detection rate or sensitivity) is in general uncertain as there is usually no follow up of those considered not to have ASDs at initial testing. Furthermore, methods to assess completeness of ascertainment in epidemiological studies have not been applied and may not be feasible (because of the expense of gathering the necessary data).

64. Attempts at identification of ASDs in the general population have varied in the degree to which they involve health professionals and collect and combine information from different sources, as well as the degree to which they employ detailed semi-standardised diagnostic procedures. For example, one recent study utilised the UK health services community paediatric surveillance procedures and a network of well-developed child development centres as a means of staged ascertainment for ASDs. Health visitors were trained to identify children with signs and symptoms suggestive of a possible ASD at the 18-month and 3½ year developmental check. Possible cases were then assessed in depth over a two week period prior to having diagnoses confirmed.

65. There are currently no thoroughly effective test instruments for the initial phase in active case ascertainment. One of the most recent and notable is the CHecklist for Autism in Toddlers (CHAT). This instrument, which comprises parental interview and child observation, picks up children on the basis of impairments in social communication and pretend play at 18 months and 3½ years. However, research to date suggests that the CHAT will detect only approximately a third of the children with ASDs in a population assessed. In addition, it will mistakenly identify as possibly having an ASD 2% of the unaffected population – a small percentage but a very large number of children.
66. Other instruments based on parent questionnaires have also been developed (e.g., the Autism Screening Questionnaire\textsuperscript{40}, the Children's Social Behaviour Questionnaire\textsuperscript{41} and the Screening Tool for Autism in Two year olds\textsuperscript{42}) and tested to varying extents, although they have not been employed in large scale epidemiological surveys of the prevalence of ASDs. No detailed comparison or evaluation of the properties of these tools in epidemiological research has been undertaken to date. Full diagnostic evaluations (e.g. with ADI-R or DISCO) are labour and resource intensive and, consequently, expensive. The implications of these issues for epidemiological research are significant; high quality investigations may only be possible in a few centres, simply because the training opportunities and relevant expertise in the UK are limited. Increased training resources would also aid standardised diagnosis for clinical services and research.

67. In addition, there are ethical issues to be considered. A population survey for ASDs would necessarily identify some individuals who had not previously been considered affected. This will be true, in particular, for those at the high-ability end of the spectrum, who might not otherwise come to clinical attention, and for whom there may be no services or treatment available subsequent to diagnosis. The ethical implications of this, and the handling of such information, require serious consideration.
4. HOW COMMON ARE AUTISM SPECTRUM DISORDERS?

68. Prevalence estimates will depend on exact assessment tools and ascertainment methods, and variations across studies will likely reflect such methodological differences. However, according to recent reviews, there appears fairly good agreement that the autism spectrum disorders affect approximately 60, and narrowly-defined autism 10-30, per 10,000 children under 8. The prevalence of autism among adult populations is not known. These estimates make autism spectrum disorders far more common than was previously generally recognised.

Prevalence and Incidence

**Prevalence** measures the number of individuals with a condition at a point in time or over a defined period. Prevalence can be established through cross-sectional surveys at specific ages. It is related to incidence and duration of disease, and may increase as a result of increasing numbers of new cases or longer survival with a diagnosis (i.e. not lost through death or reversion to ‘normality’). In turn there may be a rise in new cases because diagnostic criteria and thresholds have changed, or methods of ascertainment have improved, or because there has been a change in some causally related factor, or there has been selective migration of those more at risk of developing the disorder in question or some combination of these factors.

In contrast, **Incidence** measures the development of ‘new’ cases. Incidence is usually studied for disorders with clear onset. It is therefore potentially problematic in developmental disorders, in which age of recognition may be quite distinct from age of onset.

69. Issues of case definition (diagnosis, assessment and ascertainment) will directly affect the estimates of numbers of people affected by ASDs. Epidemiological studies of prevalence and incidence need to be distinguished (see box). For the most part, epidemiological studies of ASDs have been cross-sectional, reporting prevalence. In reviewing this area, we have drawn on two recent systematic reviews of published studies. Fombonne has collated evidence from 32 studies conducted over the last 35 years, and Wing has subsequently reported on 40 studies. Not all this earlier work will be directly referenced here and the reader is referred to the reviews for further references. Of the 40 epidemiological studies reporting prevalence as identified by Wing, 10 were conducted in the UK, emphasising the contribution made to this field by UK researchers.

70. The average prevalence from all studies published by the year 2000 is 10 per 10,000 for autistic disorder, and 2.5 per 10,000 for Asperger syndrome. Estimates from more recent studies have been higher, reflecting better ascertainment. For example, prevalence estimates based on the two most recent studies in the UK using active case ascertainment and a two stage ‘screen’ with similar criteria for caseness are consistent. Baird reported a combined prevalence of 57.9 per 10,000 in children by the age of 7th which accords with the figure of 62.6 per 10,000 for all pervasive developmental disorders reported by Chakrabarti and Fombonne in their survey of 4 to 7-year-olds in Staffordshire. Baird estimated a prevalence of 27.1 per 10,000 for Asperger syndrome which is higher than 8.4 per 10,000 reported by Chakrabarti – this may reflect some differences in age groups studied.

71. Childhood Disintegrative Disorder is very rare, with prevalence ranging between 0.1 to 0.6 per 10,000. However the five studies reporting prevalence combined included only 10 affected individuals so these estimates are very uncertain.
72. There have been two UK studies reporting incident diagnoses, and both have relied on records of diagnosed individuals. Powell et al.44 carried out a study of the incidence of childhood autism and other ASDs in pre-school children in two areas of the West Midlands between 1991 and 1996. Children diagnosed before the age of 5 years and residing within the study areas at diagnosis were detected from the records of four child development centres. The incidence rate per 10,000 children per year for the combined areas was 8.3 for all children with ASDs, 3.5 for classical childhood autism, and 4.8 for other ASDs. Kaye et al. reported an incidence of 2.1 per 10,000 person years among children aged 12 and under using data recorded in the UK General Practice Research database45.

73. ASDs used to be thought to be very rare conditions. However, the above estimates suggest that, as some investigators have always asserted, the full range of ASDs in fact affect a very significant number of children and adults.

74. A male excess is generally observed and this is especially pronounced at the high-ability end of the spectrum. Wing has speculated that this pattern reflects both greater male susceptibility to developing ASDs as well as a requirement for more severe brain involvement in girls before they express the ASD phenotype. This theory remains to be tested. It is also possible that ASDs may be harder to recognise in women, at least using current diagnostic criteria which may identify abnormal behaviours for men more successfully than for women.

75. There is currently no evidence of a social class gradient in the prevalence of ASDs47,48.

76. In the study in Camberwell49,50 the rate for “Kanner’s autism” was higher for children whose fathers were first generation immigrants from third world countries, mainly the Caribbean. In two later studies from Göteborg51,52 children with autism were significantly more likely to have parents from ‘exotic’ countries (Asia, South America, or south-east European countries). Tanoue et al.53 found a lower rate for children born in Southern Ibaraki (11.3 per 10,000) compared with that for children born in other parts of Japan whose parents had migrated into the Southern Ibaraki area (17.6 per 10,000). Ritvo et al.54 examined prevalence by ethnic origin in Utah. They found no excess of autism in children of parents of any ethnic minority, including Hispanic and Asian, but they did not report whether the parents were first or subsequent generation immigrants. Migration was not discussed in the other studies but it is unlikely that it can account for all the variation observed. There is therefore little evidence to help evaluate ethnic differences in ASDs.

77. Although very different prevalence rates have been reported from different countries it seems likely that this reflects differences in case ascertainment and case definition rather than a true between country variation in rates. Three recent studies, two from different regions of England and one from the USA, that used active case ascertainment and similar case definitions, have reported remarkably similar rates55,56,57.
Studies of Romanian adoptees who were exposed to extreme forms of early deprivation (both nutritionally and socially) suggested that environmental factors may lead to quasi-autism-like syndromes that are, however, distinguished from ASDs by their course and remission.

The issue of seasonality is a controversial area, not only for ASDs. Many psychiatric disorders have been studied with respect to seasonality, but in general the evidence remains equivocal. Whilst a few studies have reported a connection between ASDs and month of birth, most have failed to show any connection between ASDs and month of birth. A number of reasons have been proposed to explain apparent positive associations between season of birth and psychiatric disorder. At present, there does not seem to be a significant body of evidence that supports a seasonal effect on the incidence of ASDs.

Has there been an increase in ASDs over time?

Methodological differences between studies and changes in diagnostic practice and public and professional awareness are likely causes of apparent increases in prevalence. Whether these factors are sufficient to account for increased numbers of identified individuals, or whether there has been a rise in actual numbers affected, is as yet unclear, although it is evident that significant numbers of people have ASDs as currently defined.

In recent years there has been a widespread perception that the number of people coming to clinical attention with ASDs has greatly increased. Several factors, real and artefactual, may give rise to an increase in prevalence over time. These include: changing diagnostic thresholds, better case ascertainment, survival, population flows, and finally changes in the prevalence of causal factors. Methodological features associated with higher prevalence include, for example, active rather than passive ascertainment of cases, later year of publication, and studies based on smaller sample sizes. Smaller studies are more likely to use more intensive and thorough methods of case ascertainment. Changes in diagnostic threshold may affect prevalence estimates as illustrated by Heussler et al. who revised the prevalence of ASDs at age 5 years in the 1970 Birth Cohort Study from 4.5 to 3.76 per 10,000 following contemporary expert diagnostic review.

Fombonne has recently reviewed time trends in ASDs. A birth cohort analysis based on the findings of two surveys carried out in the same population suggested that within each survey the prevalence of ASD did not change according to year of birth. However, between surveys there is some suggestion of higher rates for birth cohorts which overlap – this may reflect methodological differences as well as change over time in the concept of ASDs.

The prevalence of autism among adult populations is not known. In one study, 134 adults with ASD were identified among the 893 residents of an institution for mentally retarded adults, at its closure in 1980. Only a few of the youngest residents had been previously diagnosed as having ASDs.
5. WHAT ARE THE CAUSES OF AUTISM SPECTRUM DISORDERS?

84. The causes and underlying deficits of ASDs can be defined at distinct levels. Studies of putative risk factors and markers at the biological level are distinct from and complementary to studies of the underlying psychological characteristics. The aim for research must be to uncover causal pathways from one or more possibly interacting causes, through their effects on the brain, and sequelae in the mind, to the effects in observed behavioural deficits and abilities. Such a causal pathway is as yet a distant goal, but is necessary for full understanding and development of possible preventative treatments and appropriate interventions.

85. Research over the last half century has established autism as a neurodevelopmental disorder. Early suggestions that ASDs might result from abnormal parenting have been abandoned in the face of overwhelming evidence for a biological basis and a strong genetic component. Most researchers believe that ASDs have a variety of causes, perhaps all affecting the same brain systems, or impeding development through disruption of different abilities necessary for social and communicative development. Whether environmental factors interact with genetic susceptibility is as yet unclear.

86. In assessing whether one or several factors increase the risk of developing ASDs, studies that specifically test aspects of a putative causal relationship, informed by criteria for causality, are scientifically the most rigorous. These criteria are summarised in the box (p.22). An important aspect of any assessment relates to the strength of evidence in favour of an association. Scientifically, greater weight would be given to consistency in the findings about a putative ‘cause’ for autism from several different studies that have used different methods to test a specific causal hypothesis. Studies reporting correlation, for example, that ASDs are correlated with a putative risk factor, do not of themselves provide evidence for a causal association for that risk factor, as these correlations may be unrelated causally.

87. In epidemiological terms, a cause is an “act or event or state of nature” - for simplicity, it may be referred to as an exposure - “which initiates or permits, alone or in conjunction with other causes, a sequence of events, resulting in an effect.”68. In most instances, the exposure is neither necessary nor sufficient by itself to cause the disease. Usually diseases do not have a single cause; rather, they have a constellation of component causes that, taken together, become sufficient to cause disease. For example, exposure to the chickenpox virus will not always cause chickenpox, because one must have a certain susceptibility to develop the disease or the clinical manifestations of the disease. Thus, most causes of interest are components of sufficient causes, but are not sufficient in themselves.

88. Although the box below lists criteria for causality, it should be emphasised that there are no quick and easy tests for determining causality in science. Rather a body of evidence from well-conducted studies that explicitly test causal hypotheses is required. In general, causes can be distinguished from non-causes only through studies that systematically make observations that refute one or more competing theories.
Criteria to assess Causality

- **Strength**
  - strong associations are more likely to be causal than weak associations
- **Consistency**
  - the repeated observation of an association by different studies using different methodologies and samples
- **Specificity**
  - a cause leads to a single effect, rather than multiple effects
- **Temporality**
  - the cause must precede the effect in time, with a decline in likelihood of the effect being seen with time after exposure
- **Biologic Gradient**
  - the likelihood of an effect being seen being directly related to the degree of exposure
- **Plausibility**
  - the cause has biological plausibility to produce its postulated effect
- **Coherence**
  - the interpretation of cause-and-effect fits within the known natural history and biology of the effect
- **Experimental Evidence**
  - supportive experimental testing of the underlying hypothesis
- **Analogy**
  - the weakest of the criteria, due to its subjective nature


Genetic Component to Autism Spectrum Disorders

**Possible Genetic causes**

89. Twin and family studies show that ASDs are highly heritable, although the mechanisms are likely to be complex and involve the interaction of many genes. At present, these complex genetic influences are thought to operate in most cases of ASD, while single gene disorders and chromosomal abnormalities may affect a small (5-10%) proportion of those with ASDs.

**Complex Genetic Influences**

90. In approximately 90% of individuals with ASDs, there is good evidence to indicate that complex genetic influences are contributing to pathogenesis. However, these estimates are based on studies of relatively small samples of twins that were ascertained using relatively narrowly defined and stringent diagnostic criteria. Moreover, to varying extents the samples are likely to have been subject to ascertainment bias.

Families with an autistic child are given an approximate 6% chance of having another born with the disorder. Is this a true figure and what is its significance?

91. A number of epidemiological twin studies have demonstrated the heritability of ASDs. For example, Bailey et al. found that probability of both twins having an ASD is high (60%) if they are identical (monozygotic), whereas if they are non-identical (dizygotic) the probability is very small. The rate of ASDs in singleton siblings is 2-6%, which is still at least ten times the general population prevalence.
The current consensus is that several genes may interact to create the susceptibility to ASDs. International consortia, including the British-led International Molecular Genetics Study of Autism Consortium, are searching for relevant genes. To date, the overlap in findings from the various genome screens suggest that genes will be found on at least chromosomes 2, 7, 16 and 17. There is considerable excitement about the possibility of identifying genetic susceptibility loci. Identification of genes associated with ASDs is likely to transform much of the research agenda. However, it is important to note that genes associated with ASDs may not in every case be genes responsible for ASDs – that is, they may not be part of the causal pathway. In addition, since genetic effects are often probabilistic rather than deterministic, it may be that a genetic loading for ASDs is found in some individuals without the psychological and behavioural features of ASDs, and hence any kind of genetic test for ASDs may be a very distant prospect. In recent years there has been a great deal of research into the so-called ‘broader phenotype’ for autism – subtle patterns of assets and difficulties that may be found in relatives of individuals with ASD. It is possible that carrying some of the susceptibility genes for ASDs may even confer an advantage on certain tasks. In the broader phenotype it appears that different aspects of ASDs (e.g. social difficulties, repetitive interests) may dissociate, perhaps giving clues to distinct causal pathways for these different facets of ASDs.

### Summary of Most Significant Regions of Linkage for Autism from Whole Genome Screens

The table below illustrates the chromosomes that have been independently identified as containing regions carrying potential genetic susceptibility for ASDs. There is greatest agreement for chromosome 7q, but it should be noted that the regions identified by each group are not precisely the same.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>IMGSAC, 1999</th>
<th>Phillippe et al., 1998</th>
<th>Risch et al., 1998</th>
<th>CLSA, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p</td>
<td>2.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2q</td>
<td>0.52</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6q</td>
<td>2.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7q</td>
<td>2.53</td>
<td>0.83</td>
<td>0.93</td>
<td>2.20</td>
</tr>
<tr>
<td>13q</td>
<td></td>
<td></td>
<td>0.68</td>
<td>3.00</td>
</tr>
<tr>
<td>16p</td>
<td>1.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18q</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19p</td>
<td>0.99</td>
<td>1.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values given in the table are variations on the LoD score, a measure of the probability that an identified region of association has not arisen by chance. In general, a score above 3 is considered significant, but independent replication strengthens the probability of a true association.

- **International Molecular Genetic Study of Autism Consortium (IMGSAC):** IMGSAC, Hum. Mol. Genet. 7:571-578 (1999); data expressed as multipoint maximum LOD score as determined by ASPEX
- **Paris Autism Research International Sibpair Study (PARISS):** Phillippe et al., Hum. Mol. Genet. 8:805-812 (1998); data expressed as multipoint maximum LOD score as determined by MAPMAKER/SIBS
- **Collaborative Linkage Study of Autism (CLSA):** Barrett et al., Am. J. Med. Genet. 88:609-615 (1999); data expressed as maximum multipoint heterogeneity LOD (MMLS/het) score

Table adapted from Lamb et al.81
It is possible that genetic susceptibility may interact with environmental factors to produce ASDs.

The genetic findings do not preclude the possibility that some form of gene-environment interaction may be involved in pathogenesis. That is, the presence of genetic differences may only give rise to phenotypic abnormality/differences in the presence of certain environmental factors. For example, developmental abnormalities associated with phenylketonuria (a genetic disorder) primarily arise if phenylalanine is part of the diet; simply excluding phenylalanine from the diet results in a substantially improved developmental outcome. Similar principles may apply in ASDs: a genetic susceptibility may be required, but the emergence of ASDs may depend on the presence of some as yet unidentified environmental factor. It should be noted that the environmental contribution to phenylketonuria would have been very difficult to detect without knowledge of the biological abnormalities—children with phenylketonuria are not exposed to any special environmental risk, but are genetically vulnerable to an ordinary environment.

Single Gene Disorders or Chromosomal Abnormalities

In a minority (perhaps 10%) of individuals with ASDs, there is an identifiable probable causal medical condition, usually comprising various single gene disorders or chromosomal abnormalities. These include untreated phenylketonuria, tuberous sclerosis, fragile X syndrome (FRAXA), Turner's syndrome, duplication and inverted duplication of chromosome 15q11-q15, FRAXE and possibly several other forms of chromosomal abnormality. Not included in this list is the gene mutation in MECP2 associated with Retts syndrome, as the developmental manifestations are quite distinctive, even though it is classified as a form of pervasive developmental disorder. Similarly, children with Childhood Disintegrative Disorder are occasionally found to have inherited metabolic disorders, but these constitute extremely rare occurrences.

The strength of evidence supporting claims of a specific association between genetic/chromosomal disorder and ASDs is very variable. The strongest evidence of a causal association is found for tuberous sclerosis, fragile X and inverted duplications of chromosome 15. Tuberous sclerosis may provide an important clue to brain pathology, since lesions in the temporal lobe have been shown to be a key risk factor for co-morbid ASDs. While fragile X Syndrome used to be thought to affect as many as 25% of males with ASDs, in his review estimated a far lower figure (0.75%). The symptoms shown by those with this disorder may be more properly described as 'autism like' or fitting only within the broader spectrum. An association between duplications and triplications of part of the long arm of chromosome 15 of maternal origin has been found with ASDs, often accompanied by severe mental retardation. This is of some interest as genetic studies of ASD have identified loci on the long arm of Chromosome 15. The role of mental retardation in the association needs to be investigated. In addition, sex chromosome abnormalities (Turner syndrome) have been linked to ASDs. Some 5% of females with Turner syndrome have either ASDs or features that may fall within the broader ASD phenotype. In all confirmed cases the normal X chromosome was maternal in origin. It is possible that there is increased vulnerability to ASDs in females who lack a normal paternally derived X-chromosome. Untreated phenylketonuria is nowadays so rare that the evidence for an association stems from very early studies that were undertaken before the use of well-developed and validated diagnostic criteria, although the evidence from the early reports is quite persuasive.

All told, the frequency of single gene disorders or chromosomal abnormalities in population based and clinic samples of individuals with ASDs is low and amounts to at most 5-10% of individuals. It appears that these disorders are more commonly found in individuals with atypical ASDs and moderate to profound learning disabilities. Moreover, as the concept of the autism spectrum has been broadened to include subtler forms of impairments in children of normal ability, it is likely that the overall frequency of identifiable genetic disorders will reduce.
97. In conclusion, it is well established that there is a genetic component to ASDs, although it remains unclear how many genes may be involved. In a small proportion of cases, various single gene disorders and chromosomal abnormalities have been reported in individuals with ASDs. It is entirely plausible that the autism phenotype might be derived from a number of different genetic components. One goal of current multinational genetic studies (e.g. IMGSAC, PARISS, CLSA) is to identify possible subtypes of the autism spectrum, based upon genetic evidence. Advances in genetic research are likely to play an important part in identification of any putative environmental risk factors. Genetically sensitive research designs that control for genetic effects will be necessary to investigate environmental risk factors that may be associated with ASDs.

Possible Environmental Risk Factors

98. A variety of possible risk factors for ASDs have been suggested, and were of concern to the lay members of the Review. In general, there is insufficient evidence to date to allow firm conclusions. Perinatal complications are thought more likely to be consequences rather than causes of a child’s ASD, and no specific prenatal exposures have been established as contributory. A small number of cases have been reported in which viral infection may have played a role. We conclude from our review that the current epidemiological evidence does not support the proposed link of MMR to ASDs. Our conclusions are consistent with the previous MRC Reviews and with the findings of other expert groups that have reviewed this question.

99. The following section discusses potential environmental risk factors that might be relevant. It must be stressed that the term “environmental” implies all factors other than genetic susceptibility. At present there is little, if any, direct evidence in support of these potential factors. Many of these factors are ones that have been suggested by the Lay Group, or are the subject of speculation in the community.

Suggested Prenatal Risk Factors

‘Are there factors in pregnancy, for example intrauterine infections, or in the perinatal period, which might be associated with an increased risk of autism spectrum disorders?’

100. In determining the causal role of putative infections or exposures operating in pregnancy or shortly after birth, the direction of any observed associations cannot always be assumed to be causal. For example, there may be a shared genetic predisposition to obstetric complications as well as ASDs. Case control studies are the most efficient study design to examine this but need to be interpreted with care in relation to assessment of factors that depend on retrospective recall.

101. The available evidence suggests that while there may be some suggestion that pre and peri-natal problems may be more common in children with ASDs, the associations reported appear to be non-specific, inconsistent and do not help to identify a sub-group who are at meaningfully increased risk of later ASDs. This inconsistency reflects in part the variation in the factors reported in different studies as well as their small sample size and variable definition of ASD. There is some evidence to suggest that there is an increase in mild obstetric complications, but this is considered unlikely to be causally relevant. No association of obstetric complications with severity of ASDs has been found in one study based on children with tuberous sclerosis and ASDs.
Drugs

102. There are reports in the literature that ASDs may be associated with in utero (prenatal) exposure to thalidomide\textsuperscript{116,117}; valproic acid\textsuperscript{118}, supported by animal experiments\textsuperscript{119}, and other anticonvulsants\textsuperscript{120}; cocaine\textsuperscript{121}; and possibly alcohol\textsuperscript{122,123}. Of these, the association with thalidomide is the strongest, and was the rationale for a genetic study in autism\textsuperscript{124}. It should be noted that thalidomide has been contra-indicated in pregnancy for many decades.

Endocrine factors

103. The fact that ASDs occur more frequently in males than in females raises the possibility of a role for sex hormones in the development or expression of autistic traits. Oestrogens and progesterone have been reported to have neurological functions (such as to reduce the consequences of brain injury, appearing to function as neuroprotective and neuroregenerative agents on stroke and traumatic brain injuries\textsuperscript{125,126}). The implications of this research are that if environmental or genetic factors (or their interaction) cause damage to the developing brain, this damage might be ameliorated by the presence of oestrogen and progesterone. Thus females would be expected to show fewer sequelae of neural damage than males. Similarly, if sex hormone levels in males at critical times of development were abnormal, there could conceivably be adverse consequences for neural repair, regeneration and/or development, which may include ASDs. However this theory remains highly speculative, and is not supported by any direct evidence.

Carbon monoxide

104. Anatomical malformations as well as functional and psychomotor disturbances have been seen in the offspring of mothers who have experienced carbon monoxide (CO) poisoning. Low-level chronic exposure to CO is probably much more common than currently suspected. It is known that pregnant women and their foetuses are particularly susceptible to the hypoxic impacts of carbon monoxide because of the mother's increased rate of endogenous CO production, the contribution of the foetus' endogenous production, and a 20-30% reduction in the mother's oxygen carrying capacity. The foetus is highly sensitive to any decrease in oxygen carrying capacity and often dies even when the mother survives CO intoxication with no adverse effects herself. Whilst it is biologically plausible that such neurological insult may affect brain systems associated with ASDs, there is no evidence in support, and this theory must remain extremely speculative.

Risk Factors in Childhood

Infections

105. No cases have been reported of direct bacterial, parasitic or other non-viral infection in the CNS that were associated with patients displaying ASD symptoms. Effects of alteration in the gut flora are discussed below.

106. In contrast, a role for viral infection in triggering ASDs has been proposed in a number of studies. ASDs has occasionally been associated with cases of perinatal cytomegalovirus infection\textsuperscript{127,128} in children as well as with cases of congenital rubella infection\textsuperscript{129,130}. A small number of cases have been described associated with herpes simplex virus encephalitis\textsuperscript{131,132}. All these viral infections have many other detrimental effects on the brain of infected patients and hence it is probably not
surprising that some of the affected children displayed symptoms associated with autism spectrum disorders. With the disappearance of congenital rubella the number of reports of associated ASD has decreased substantially. The cases were sporadic and rare and hence it is unlikely that these viruses act as triggers for the majority of individuals with ASDs.

107. A potential link between ASDs and infection was suggested by a paper by Wakefield et al. in 1998. On the basis of an “early report” of twelve individuals, the authors implied that exposure to the combined measles mumps rubella vaccine was a risk factor in ASDs and they described in these children a disease which they called ileal lymphoid-nodular hyperplasia. The issue of gastrointestinal inflammation in autism spectrum disorders is considered elsewhere in this report. A report appeared in 2000 that provided reverse transcriptase polymerase chain reaction (RT-PCR) evidence for the presence of measles virus RNA in peripheral blood mononuclear cells of ileal lymphoid-nodular hyperplasia, or “autistic enterocolitis”, patients in samples provided by Dr Wakefield’s group. However, the authors also found RNA of measles virus in the same tissue from patients with ulcerative colitis and Crohn’s disease. These papers also rekindled interest in studies by Singh and collaborators that showed that measles and human herpes virus 6 antibody levels in sera of children with ASDs were elevated, though not out of the normal range. Singh and his colleagues had also showed a correlation between anti measles titres and levels of anti-myelin basic protein antibodies. However, at present there is no evidence for inflammation or histological responses to infection or for demyelination in the CNS of patients with ASDs. Reports of immunological abnormalities in children with ASDs have been many and variable and no conclusive picture emerges, especially as many confounding factors have been inadequately controlled in the majority of studies.

Borna disease

108. This virus is an agent responsible for a disease in horses limited to Central Europe, which has been characterised only during the last decade, leading to the possibility of tracking any infection by antibody tests and detecting the viral genome by RT-PCR. The evidence for human infection with Borna Disease virus is extremely controversial. A recent review by Staeheli and colleagues suggests that many researchers have probably fallen foul of the contamination problems that occur when RT-PCR technology is driven to the limits of sensitivity. Furthermore, the serological evidence is questionable because non-standardised testing protocols gave rise to differing percentages of positive sera in various groups of patients. The evidence for human infection with this agent is thus weak. Epidemiological studies of the virus have relied on these difficult methods and have led to the conclusion that the virus is more wide spread than originally thought. Infection in animals other than horses appears to give rise to very little clinical disease. Borna disease virus infection in neonatal rats has been suggested as an animal model for ASDs. The intracerebral injection model in neonatal Lewis rats has several features that are similar to, and others that differ from ASDs, e.g. the presence of inflammation. Whether the behavioural traits and motor disturbances in the rats are similar to those of human patients is debatable. More stringent studies, involving RT-PCR to detect genomic or anti-genomic RNA, are required to establish whether the virus is an infectious agent associated with any of the neuro-psychiatric illnesses such as schizophrenia, bipolar disease, Obsessive-Compulsive Disorder and ASDs in which it has been proposed to play a role so far.
Some viruses can remain dormant in the body over long periods, but there is no evidence as yet for a link to ASDs or other disorders.

Persistent infection

109. It has been hypothesised that ASDs may be causally related to the existence of persistent infection. Many viruses, such as herpes simplex, varicella zoster, and Epstein-Barr virus, persist in the human body throughout life. These viruses are all large DNA viruses, with a very stable genome that is able to be maintained or be latent in the cells that harbour them, which allows their presence not to be detected by the host immune system. At present there is no evidence that such persistent infections are causally related to autism.

110. Measles, mumps and rubella viruses are all RNA viruses, with much less stable genomes that may need to replicate to maintain infection. The sites at which persistent replication of these viruses would take place are likely to be immuno-privileged. Only for measles virus is there good evidence that it can persist, and cause subacute sclerosing panencephalitis (SSPE), a very rare disease which gives rise to a fatal brain infection with mutated forms of measles virus about eight years after the initial infection. However no site for the persistence of measles virus has yet been convincingly identified. Measles virus has been a prime candidate as a causative agent in many diseases of unknown aetiology. However, apart from SSPE, there is no definitive evidence that it is associated with diseases such as autism, Paget’s disease; Crohn’s disease, autoimmune chronically active hepatitis; multiple sclerosis, diabetes, lupus erythematosus, or otosclerosis.

Immunisations

‘Does further evidence published since the last MRC review and specifically examining possible associations between MMR and ASDs alter the conclusions of that review?’

111. A number of expert review groups have considered the specific question of the potential link between MMR vaccination and ASDs (the Medical Research Council, the American Medical Association, the Institute of Medicine, USA, the World Health Organisation, the American Academy of Pediatrics, the Population and Public Health Branch of Health Canada, and the Irish Department of Health and Children). All of these groups have analysed the published work, including that outlined in the previous section. Several or all of these reviews have included material from oral presentations by Dr Wakefield and his collaborators in which they outlined new information relating to their proposal for a link between MMR and ASDs. It is not the function of the present MRC Autism Review to revisit and reconsider previous expert opinion.

112. The aforementioned reviews were unanimous in their conclusions that a causal link between the MMR vaccine and “autistic colitis” and ASDs was not proven and that current epidemiological evidence did not support this proposed link. The Institute of Medicine report noted that “this conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children, because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD”. We recognise that, as with most epidemiological studies of causation, this remains a theoretical possibility. More extensive research would be necessary to provide evidence for the biological plausibility of a suggested causal link between viral infections and ASDs (as this is currently not robust), as it would be for other proposed causal factors.

113. In this section we review epidemiological studies addressing the putative association between MMR and ASDs that have been published since the last MRC review of this topic. These studies have been grouped by country of origin. It is important to recognise that epidemiological studies...
cannot prove that vaccines are safe but can only exclude specified adverse effects with a certain
degree of confidence. As has been discussed earlier in this section, studies that have specifically
tested aspects of a putative causal relationship that are informed by criteria for causality are
scientifically the most rigorous [See text box on causation p.22]. Currently there are no
epidemiological studies that provide reliable evidence to support the hypothesis that there
might be an association between MMR and ASDs.

**UK studies**

114. Taylor et al. and Farrington et al. reported findings from their study in North London which
examined the potential association of MMR and ASDs\(^1\). Case and time series methods were used
to investigate clustering of cases of ASDs within defined post immunisation periods as well as to
investigate potential effects of second dose of MMR. 498 cases of ASDs were identified (261 of core
autism, 166 of atypical autism, and 71 of Asperger’s syndrome). In 293 cases the diagnosis was
confirmed by ICD-10 criteria: 214 (82%) core autism, 52 (31%) atypical autism, 27 (38%) Asperger’s
syndrome. There was a steady increase in cases by year of birth with no sudden “step-up” or
change in the trend line after the introduction of MMR vaccination. There was no difference in age
at diagnosis between the individuals vaccinated before or after 18 months of age and those never
vaccinated. There was no temporal association between onset of ASDs within 1 or 2 years after
vaccination with MMR (relative incidence compared with control period 0.94 [95% CI 0.60-1.47]
and 1.09 [0.79-1.52]). Developmental regression was not clustered in the months after vaccination
(relative incidence within 2 months and 4 months after MMR vaccination 0.92 [0.38-2.21] and 1.00
[0.52-1.95]). No significant temporal clustering for age at onset of ASDs within 1 or 2 years after
vaccination with MMR (relative incidence compared with control period 0.94 [95% CI 0.60-1.47]
and 1.09 [0.79-1.52]). Developmental regression was not clustered in the months after vaccination
(relative incidence within 2 months and 4 months after MMR vaccination 0.92 [0.38-2.21] and 1.00
[0.52-1.95]). No significant temporal clustering for age at onset of parental concern was seen for
cases of core autism or atypical autism with the exception of a single interval within 6 months of
MMR vaccination. This appeared to be an artefact related to the difficulty of defining precisely the
onset of symptoms in this disorder. In a subsequent publication\(^1\) further analyses were published
testing different (longer) induction intervals as well as the effect of a second dose of MMR. Again
no association was found, providing further evidence against a causal association between MMR
vaccination and ASDs. This study was large, well designed and employed a novel but appropriate
statistical methodology. Although it relied on diagnoses made in routine health care, this is only
likely to have biased assessments of association if these diagnoses were in some way more or less
likely to have been made in those who had received MMR. At the time this study was carried out,
this was unlikely.

115. There have been two publications reporting studies which have examined or will be examining
associations between MMR and ASDs using the same General Practice Research database\(^1\). The
first publication reported an analysis of the incidence of ASDs in relation to the timing of MMR and
concluded that there was no association. It is likely that in this study there was substantial under-
ascertainment of ASDs as the estimated frequency of ASDs seemed very low. Furthermore there
was no validation of the diagnoses recorded\(^1\).

116. Before this report was published, the MRC had funded a case control study based on the same
database and the protocol for this has been published\(^1\). This study will use control participants
as well as cases, and will also examine time sequences of events using time series analyses. As a
method of validating diagnoses is planned, it is potentially of higher quality than the other study,
but results are not yet available.

117. A further study using yet another routine GP database has been published recently\(^1\). The
authors proposed that if there were a close temporal association between MMR vaccination and
loss of skills/onset of ASD then this would be reflected in increased consultations with the child’s general practitioner. The Doctor’s Independent Network database was used to examine whether children subsequently diagnosed as autistic consulted more frequently than controls after MMR vaccination. No difference in consulting behaviour was seen in the six months post MMR and the authors concluded that any dramatic effect of MMR on behaviour seems unlikely.

118. A recently published study has examined the hypothesis that MMR is associated with a new phenotype of ASD combining developmental regression and gastrointestinal symptoms. Findings from a recent study carried out in Staffordshire were compared to those reported from two previous studies, one performed before the combined MMR vaccine was introduced. These comparisons were made in order to investigate, in those exposed and not exposed to MMR, the age of first parental concern, the temporal relation of onset of regressive autism to MMR, the relation of regressive autism to gastrointestinal symptoms, and the symptom and severity profiles of those with regressive autism. Mean age at first parental concern was virtually identical in the MMR and non-MMR groups, as was the proportion with regressive autism. No phenotypically distinct features were found in those reported as having regressive autism. Mean interval between MMR and parental recognition of autistic symptoms did not differ in children with or without regression. No case of inflammatory bowel disorder was identified and there was no association between developmental regression and gastrointestinal symptoms. This study overcomes some of the problems of potential selection bias, which might occur in other studies relying on routine data. It provides additional evidence that an association is unlikely.

119. An observational study was reported very recently based on a case note review, by Canadian and UK researchers, of the notes of 900 UK children whose families are taking legal action on the basis that MMR was associated with their child’s ASD. The published report provides only very limited information about study methodology and design. Following detailed case note review for 493 of these 900 children, 124 subjects were excluded as ineligible, either because the diagnosis of ASD was in doubt, because ill health preceded MMR, or in the case of two children, because onset of symptoms occurred within 30 days of MMR. Of the remaining 369, 325 were considered to have a definite or probable diagnosis of ASD, although the method of assigning diagnosis from review case notes was not specified. Based on retrospective assessment of medical records, 112 of these children (39%) were deemed to have regressed from normal function, prior to MMR, to major developmental delay. Median time to symptoms from MMR was 1.1 years, but from MMR to diagnoses was 2.5 years (interquartile range 1.8 to 4.2 years). There were no control participants. The authors acknowledge the self-selected and unrepresentative nature of this group but, somewhat surprisingly, consider this unlikely to introduce bias when estimating distribution of time intervals between MMR and ‘onset’ of ASDs. The only conclusions that may be drawn from this study are that MMR is given at 15-18 months and the average age at diagnosis of autism in the UK is about 4 years.

North American study

120. A study from California has been published looking at health service registrations. This involved a retrospective analysis of MMR immunisation coverage rates among children born in 1980-1994 who were enrolled in California kindergartens (survey samples of 600-1900 children each year). School immunisation records were reviewed to determine retrospectively the age at which they first received MMR immunisation. ASD caseloads were also analysed among children born in these years who were diagnosed with ASDs and were enrolled in the California Department of Developmental Services regional service center system. No correlation was found
between the secular trend of early childhood MMR immunisation rates in California and the secular trend in numbers of children with ASDs enrolled in California’s regional service center system. For the 1980-1994 birth cohorts, a marked, sustained increase in ASD case numbers was noted, from 44 cases per 100,000 live births in the 1980 cohort to 208 cases per 100,000 live births in the 1994 cohort (a 373% relative increase), but changes in early childhood MMR immunisation coverage over the same time period were much smaller and of shorter duration. Immunisation coverage by the age of 24 months increased from 72% to 82%, a relative increase of only 14%, over the same time period. These data do not suggest an association between MMR immunisation among young children and an increase in ASD occurrence.

**Finnish study**

121. This study examined gastrointestinal symptoms reported prospectively as adverse events in temporal relation to MMR vaccine151. The authors subsequently traced those vaccinated children who developed gastrointestinal symptoms or signs lasting 24 hours or more at any time, apart from the first hour, following vaccination. The health records of these subjects were examined in order to determine whether any of those children with gastrointestinal symptoms later developed ASDs or other neurological signs or symptoms. The authors identified 31 cases of gastrointestinal symptoms, which were reported as adverse events, out of ~3 million vaccination episodes. No child had developed an ASD when followed at an interval of about 9-10 years after immunisation. Two children developed meningitis within 1-2 weeks after vaccination, while a third was diagnosed as having a rare inherited neurological disease some 8 years later. This study did not find any evidence to support an association between MMR and either gastrointestinal symptoms or later onset of ASDs in those with earlier gastrointestinal symptoms. However, this particular report did not examine the relation of MMR and ASDs irrespective of gastrointestinal symptoms and does not therefore provide useful evidence on this point.

122. The same group of investigators subsequently published152 further data from their investigation of prospectively reported adverse events following MMR vaccine in 1.8 million individuals. Over a 14 year period, 173 potentially serious reactions claimed to have been caused by MMR were identified; in 77 these involved the nervous system, and in about half subsequent investigation revealed another probable cause. The authors concluded that serious adverse events following MMR are rare. While this latter publication is based on very large numbers, the findings need to be interpreted with some caution as cases of ASD or bowel disorders not considered at the time attributable to MMR would not necessarily have been reported.

123. On the basis of these studies, the MRC Autism Review concludes that the current epidemiological evidence does not support the proposed link of MMR to ASDs. Our conclusions are consistent with the previous MRC Reviews and with the findings of other expert groups that have reviewed this question.

**Other Suggested Environmental Risk Factors**

**Mercury**

124. Exposure to mercury during the critical periods of early development can lead to a variety of developmental problems affecting motor skills such as walking and speech153. It has been suggested that some of the sensory, neurological, motor, behavioural and other dysfunctions associated with mercury intoxication are similar to traits associated with ASDs. Methyl mercury is the form most commonly associated with risk of developmental effects. In serious cases of methylmercury exposure of the developing foetuses, the effects can be delayed, including retardation of
developmental milestones such as walking and talking and more severe effects such as brain damage with mental retardation, incoordination and inability to move can occur in extreme cases.\textsuperscript{114} There have been suggestions that early exposure to thiomersal (called ‘thimerosal’ in the US), a preservative containing approximately 49% ethylmercury that has been used successfully as a preservative in vaccines, may be implicated as a risk factor for ASDs.\textsuperscript{115} It is worth noting that there is no thiomersal (or other mercury) in the MMR vaccine as currently administered. Ethylmercury is a less common form of organic mercury than methylmercury, which is known to accumulate in the environment. It is less easily bound to tissues than methylmercury, but does similarly biotransform to inorganic mercury.

Although there are apparent similarities between symptoms characteristic of ASDs and mercury poisoning, there is no evidence for elevated levels of mercury in children with ASDs. A study of 14 trace elements (including mercury) in hair samples from normal and children with ASDs showed significantly lower calcium, magnesium, copper, manganese and chromium, and higher lithium levels in children with ASDs than controls; there was no difference in measured mercury levels.\textsuperscript{116}

The Institute of Medicine of the National Academies has recently reported on thiomersal usage (www4.nationalacademies.org/news.nst/isbn/0309076366). The committee’s comprehensive assessment of the scientific literature on thiomersal included analyses of published and unpublished studies proposing an association with disorders such as ASDs, and found them to be inconclusive. No evidence currently exists that proves a link between thiomersal-containing vaccines and ASDs, attention deficit-hyperactivity disorder, speech or language delays, or other neurodevelopmental disorders.

A recently reported study in the UK by Lewendon et al.\textsuperscript{117} found that children with behavioural and/or developmental problems have higher blood lead levels than controls. There was a statistically significantly higher proportion of children with lead concentrations above the commonly accepted ‘safe’ level in ‘cases’ compared to controls. These differences were not explained by differences in age, sex or socio-economic status. It is not known whether this is a causal or non-causal relationship, and its relevance to ASDs is, at present, unclear.

Suggested Physiological Abnormalities in ASDs

There has been considerable interest in a number of suggested physiological abnormalities, affecting the gastro-intestinal tract, sulphation and immune system. Casein and gluten-free diets have been tried, with some reports of improvements. Data are presently limited, and further research, including appropriate control groups, would be of value. Neurochemical studies suggest possible abnormalities in the serotonin system, but further research is needed. The association between ASDs and epilepsy (which affects approximately 30%) should give clues to possible causes, but requires further study.

The Gastro-Intestinal Tract

There has been considerable interest in the possibility that there are significant gastrointestinal problems in individuals with ASDs. It has been postulated that altered intestinal permeability can result in adverse events occurring in the central nervous system, which might result in
developmental regression. However, it remains unclear whether such compromised gastrointestinal function is a cause of ASDs, or whether it reflects one facet of the disorder in a subpopulation of affected individuals. At present there are no epidemiological data at the population level to indicate the incidence or prevalence of gastrointestinal problems within the population of individuals with ASDs.

Inflammatory changes and the intestine

131. The question of “autistic enterocolitis” was first suggested in the series of 12 children reported in the Lancet in 1998133, which was the subject of considerable debate, both within the Lancet itself and elsewhere. Since that time further reports by the Royal Free group have studied changes in the intestine in relation to ASDs, as a separate issue from MMR vaccination. Rather, changes in the small bowel in children with ASDs are now being studied in the context of a general phenomenon where certain neurological syndromes are associated with intestinal pathology. A typical example of such a condition is Batten’s disease, which is diagnosed by the presence of lipofuscinosis on rectal biopsy.

132. The original Lancet paper was not considered in detail for the purposes of this Review, having been the subject of previous MRC working groups2. However, in two subsequent reports, the investigators examined the intestine of children with autism spectrum disorders, both macroscopically and microscopically. In the first, Wakefield et al.138 examined 60 children with neuronal developmental disorders: fifty had autism, five had Asperger’s syndrome, two had a disintegrative disorder and one an attention deficit disorder. Cases had been referred to a gastroenterology unit with an interest in ASDs. 22 children studied for gastrointestinal symptoms sufficient to warrant endoscopy, but who displayed no recognisable intestinal abnormality, served as controls. In addition, 20 children with ulcerative colitis were studied. The article reported a significant increase in lymphoid nodular hyperplasia (LNH) in both ileum and colon in the affected children compared to controls. Microscopically, there was increased reactive follicular hyperplasia in ileal biopsies. 8% of the affected individuals had active ileitis, but none of the controls. An effort was made to avoid observer bias of the histology and 10 biopsy series were independently assessed in an observer-blinded fashion at a separate institution. Caution, however, must be exercised in extending these observations to all children with ASDs because of the selection bias of the sample (referral to a paediatric gastroenterologist). Furthermore, the study did not examine the changes in children with many years of chronic constipation, but without neurological impairment. These problems will not be easy to address because of the ethical considerations of performing ileocolonoscopy in either neurologically normal children with long-term constipation, or in children with ASDs without bowel symptoms.

133. The second study by Furlano et al.139 examined the histology of 21 children with autism spectrum disorders and compared them to 8 children whose ileum and colon were histologically normal, 10 developmentally normal children with ileal lymphoid nodular hyperplasia, 15 with Crohn’s disease and 14 children with ulcerative colitis. The report examined the hypothesis that the lymphoid nodular hyperplasia in autism spectrum disorders was part of a general intestinal pathology, unlike lymphoid nodular hyperplasia observed in children with non-specific abdominal symptoms or with constipation, atopy, and low immunoglobulin concentrations. The authors reported specific histological changes in the children with ASDs. These included an increase in basement membrane thickening. There was also an increase in lamina propria T cells, particularly those expressing γδ or CD8. There was an increase in intraepithelial lymphocytes in the children with ASDs. Epithelial cells expressed increased HLA-DR and increased proliferation suggesting
A number of studies have found intestinal abnormalities in people with ASDs. Whether these are more common than among non-ASD people who have comparable eating and bowel habits is unclear. There is little published evidence on gut permeability in people with ASDs.

stimulation by immune derived factors. The inflammatory changes were subtle compared to Crohn’s disease. This was reflected in a lack of increase in serum inflammatory markers in the children with ASDs. It also pointed to a process that does not involve interleukin 6 stimulation. These findings suggested the possibility of lesions of the intestine in children with ASDs. However, questions of the effect of long-term constipation on the gut and changes in the intestine in children without bowel symptoms were not considered in this study. Again, the ethics of examining the histology of such controls may be problematic. Furthermore, the differences between the groups were small and the statistical methods used may not have been entirely appropriate.

134. Horvath et al. studied the upper gastrointestinal tract in children with autism spectrum disorders. The results of this group did not overlap with those of the Royal Free group because none of the 37 children studied underwent colonoscopy. However, the authors did report a greater than expected incidence of oesophagitis, gastritis and duodenitis. An interesting new observation was an increase in the number of Paneth cells in the small intestine compared to controls or to HIV infected children. Another feature was increased production of pancreatico-biliary fluid following secretin stimulation in children who had ASDs and diarrhoea when compared to children with ASDs and no abdominal symptoms. These studies again suggest a possible change in the gastrointestinal tract for individuals with ASDs.

135. In summary, since 1999, a small number of articles have reported there to be a specific gastrointestinal pathology for ASDs. However, caution must be exercised in extrapolating from results seen in children referred to a paediatric gastroenterology unit to ASDs generally, for the reasons given above. Furthermore, the most informative control groups, children matched for abnormal eating behaviour and/or degree of constipation, should have been investigated.

Intestinal permeability
136. There is little published data on intestinal permeability in ASDs. Only one study of sugar permeability has been published. D’Eufemia and colleagues reported increased lactulose/mannitol ratios after sugar challenge in 9 of 21 patients with ASDs. This was significant, as none of the control group had raised sugar permeability ratios. The changes in ratios were due to an increase in lactulose permeability, rather than reduction in mannitol absorption. The histological basis for these changes was not studied. However children with other pathology that could result in increased permeability were excluded from the study. For example, children with atopy, coeliac disease, giardiasis and Helicobacter infections did not enter the study. It could be argued that the changes in lactulose permeability may be due to changes in the small bowel. Because lactulose is metabolised in the large bowel by colonic flora, it is not available for colonic permeation.

137. Further data on permeability are required because a proposed mechanism of neuronal damage in children with ASDs depends on the assertion that casomorphin is taken up in increased amounts by the intestine of individuals with an ASD. Not only is the evidence for permeability defects poorly established, but also sugar permeability is a poor predictor of peptide and protein permeability.

Nutrition and Diet
138. The nutrient intake of children with ASDs as a group has been found to be adequate and typical of well-fed American children; these children showed no evidence to toxicity or deficiencies in the minerals or nutrients studied.
There are a number of single case reports of clinical improvement in children with ASDs placed on gluten and/or casein free diets. However, McCarthy and Coleman had reported a study of 8 children with autism on a gluten-free diet, who all had steatorrhea and hypocalciuria. They were challenged with 20g of gluten/day for 4 weeks. No gross changes in behaviour, appetite, body weight or bowel habits were seen; further, no abnormal pathologies were seen in jejunal biopsies. A recently published abstract reported on Medline would indicate that further studies are in progress, but to date they report that 46-50 children with ASDs showed an improvement in behaviour and gastrointestinal symptoms when placed on gluten & casein free diet. These investigations are based upon studies reporting that during proteolysis of casein in the gastrointestinal tract $\beta$-casomorphines were created, and that they were biologically active with both endorphin effects and immunoregulatory properties. Similar glucomorphins were also produced from wheat proteins.

Although it is possible to provide a plausible biological hypothesis to explain the possible beneficial effects of gluten and casein free diets in ASDs there are to date no properly controlled studies described in peer-reviewed journals. Given the publicity surrounding these reports and, if substantiated, the potential widespread benefits, it is important that properly controlled studies should be undertaken to clarify the situation.

Abnormalities in the composition of the enteric flora have been suggested to occur in ASDs, and antibiotic and antifungal therapies have been used – although usually in commercial, non-academic, centres. Such suggestions of enteric dysbiosis were initially based on reports of the onset of ASDs after antibiotic treatment for otitis media. There remains a dearth of hard data in the peer-reviewed literature. In particular there are so far no published studies examining the flora in children with ASDs.

A leading proponent of the theory that bacterial and fungal overgrowth contributes to autism spectrum disorder has been Dr William Shaw, who runs a commercial laboratory offering private stool analysis at the Great Plains Laboratory in the USA. However, the peer-reviewed literature on this topic is currently limited and based on indirect evidence. In two siblings with a variant of ASD associated with skeletal muscle weakness, high urinary tartaric acid and arabinose secretion was detected by gas chromatography and mass spectrometry, potentially due to overgrowth of Candida albicans. Both the muscle weakness and cognitive abnormalities were reported to respond to anti-candidal therapy, and tartaric acid concentrations decreased significantly. However, the potential neurotoxicity of candidal metabolites remains speculative and largely under researched. There have been reports of production of various gliotoxins by Candida albicans. It is not clear that it is valid to extrapolate this limited data to the wider autism spectrum and thus, at present, anti-candidal therapy cannot be considered to be evidence-based.

One bacterial species which has been suggested as pathogenic in ASDs is Clostridium tetani, with cognitive abnormalities proposed to be induced by the action of clostridial neurotoxins absorbed from the intestine. Shaw’s laboratory has also reported increase in urinary tyrosine metabolites, which have been interpreted as suggestive of Clostridial overgrowth. Sandler, Finegold and colleagues have recently reported on a pilot study of oral vancomycin therapy in children with regressive ASDs. Evidence of significant cognitive improvement was reported with vancomycin therapy, assessed by formal psychological assessment and study of video recordings, with regression...
about a week after the course of antibiotics finished. This preliminary report provides probably the most significant support for the concept that dysbiosis may occur in children with ASDs, but is, of course, indirect.

144. Similar cognitive improvement in 5 children has been reported, although not in peer-reviewed publication, by Borody, using the Rask-Madsen technique of colonic bacteriotherapy – the instillation of donor faecal flora (apparently, usually the father’s) containing non-toxigenic clostridial species after a period of gut-sterilising antibiotics. These reports cannot be critically evaluated until formal publication.

145. The MRC Autism Review has been made aware of a follow-up to the Chicago study by Finegold, in collaboration with Professor Glenn Gibson and colleagues (Food Microbial Sciences Unit, University of Reading, UK) investigating the flora in 200 American children with ASDs. This study has apparently employed the appropriate molecular technology (selective media, gut model fermentation, 16s RNA analysis, FISH), and does suggest unusual patterns of overgrowth of Clostridia species and Candida albicans (G. Gibson, personal communication). Publication of this study should provide much needed data for focused intervention studies.

146. In conclusion, this is an area where speculation currently outweighs published literature. The number of peer-reviewed papers on this topic is small, although tending to suggest that abnormal colonisation may occur. One major study is largely complete and, when published, may have a significant impact on the field.

**Sulphur Metabolism**

147. Interest in this area has been prompted by reports of impaired sulphate processing in children with ASDs, mainly from the group of Waring et al. The process of sulphation within mammalian tissues requires the presence of a suitable sulphate donor, a sulphotransferase enzyme and an appropriate acceptor. The sulphate donor, as far as is known, is always 3’-phosphoadenosine-5’-phosphosulphate (PAPS). There are a range of sulphotransferase enzymes which have specificity for different acceptors, such as phenol sulphotransferases and carbohydrate sulphotransferases.

**Generation of the sulphate donor**

148. Relatively little sulphate is absorbed from the diet, although sulphites added as preservatives may contribute substantially. It is thought that sulphate is predominantly generated in the human from sulphur-containing amino acids such as cysteine by the process of sulphoxidation (reviewed by McFadden). A study by Waring et al. reported the development of an assay for this process using S-carboxymethyl-L-cysteine (SCMC) as the substrate. They described genetic variants or polymorphisms in this process. They report that in their subject population 65% were good metabolisers, 32.5% poor metabolisers and 2.5% non-metabolisers. However, there have been a number of criticisms of the assay, also reviewed by McFadden. A study by Brockmoller et al. reported that urinary elimination of SCMC as carboxymethyl-L-cysteine sulphone did not amount to more than 1% of the test dose in any of 33 normal volunteers tested, nor was there any evidence of polymorphism. Similar concerns were raised by Meese and Fischer and Kupfer and Idle.
Using an assay which they developed for assessment of cysteine oxidation, Waring and collaborators have reported reduced sulphoxidation in patients for a variety of conditions (food sensitivity\textsuperscript{186}; systemic lupus erythematosus\textsuperscript{187}; Alzheimer’s disease\textsuperscript{188}; arthritis patients with D-penicillamine toxicity\textsuperscript{189}; and individuals with jaundice after chlorpromazine\textsuperscript{190}). They have also reported low ratio of sulphate to cysteine in motor neurone disease and Parkinson’s disease\textsuperscript{191}. These findings remain to be replicated. Furthermore there appears to be some inconsistency in these findings, as an early report of impaired sulphoxidation in 84% of patients with primary biliary cirrhosis\textsuperscript{192} contrasted with a later report from Waring and colleagues which reported impaired sulphoxidation in only 26% of patients with primary biliary cirrhosis, similar to the rate (25%) in healthy controls\textsuperscript{193}. Waring and colleagues have reported reduced urinary excretion of sulphate in children with ASDs\textsuperscript{194}, and are cited by McFadden\textsuperscript{179} as finding reduced metabolism of SCMC in children with ASDs\textsuperscript{195,196}. These findings remain to be independently replicated.

**Phenol sulphation**

One key role of sulphation pathways is the detoxification of phenolic compounds (e.g. catecholamine neurotransmitters, steroids including oestrogens and progesterone, bile acids and many phenolic drugs) which occurs both in the liver and in the intestine. Impaired phenol sulphation has been reported by Waring and colleagues in ASDs\textsuperscript{197,198}, but also in rheumatoid arthritis\textsuperscript{199}, Alzheimer’s disease\textsuperscript{188}, Parkinson’s disease and motor neurone disease\textsuperscript{200}. The assay used by Waring \textit{et al.} entails administration of an oral dose of paracetamol followed by urine collection and measurement of paracetamol sulphate and paracetamol glucuronide. However, there are a number of issues over this specific assay as data are published as a ratio of paracetamol sulphation to glucuronidation so it is not possible to determine whether the abnormality is reduced sulphation or, in fact, increased glucuronidation. Further, sulphation and glucuronidation were deduced indirectly from assay of paracetamol before and after treatment with sulphatase or glucuronidase enzymes. However the sulphatase enzyme used (Sigma S-9626) itself has considerable glucuronidase activity, which has to be inhibited by addition of D-saccharic acid 1,4 lactone. The reproducibility of this assay was not stated and nor the completeness of the enzymatic desulphation or deglucuronidation processes. In the absence of direct evidence, other explanations, including reduced phenol sulphotransferase activity, need to be considered as well as the proposed defective generation of sulphate from cysteine.

There are two types of phenol transferase, thermostable enzymes which act on simple phenols, and thermolabile enzymes, which act on catecholic or phenolic monoamines (such as dopamine and tyramine). The genes for 3 of these enzymes are known and have been sequenced (SULT1A2hum, SULT1A1hum and SULT1A3hum). Waring’s group have reported that both thermostable and thermolabile forms are polymorphic and both act on paracetamol as a substrate\textsuperscript{179}. Recently a new colorimetric assay for phenol sulphotransferase (in platelets) using 2-naphthol as substrate has been reported\textsuperscript{201}, which seems to be a more robust assay as it was possible to correlate the results of this assay with genotype.

In conclusion, the impaired sulphation story in ASDs is potentially biologically plausible but remains unproven. There are published data from only one group (Waring \textit{et al.}) reporting impaired sulphation in ASDs, using indirect methods of assay. There is a need for independent replication of these findings to be published, preferably using more direct methods of assay.
There is considerable interest in possible immune problems in ASDs, but there is a lack of published research in this area.

**Immune Function**

153. The issue of immunological abnormalities in ASDs has been widely debated, but there is a lack of reports in the peer-reviewed literature. Studies of immunological function in children with ASDs have reported a wide array of abnormalities, including decreased cellular responses, decreased serum C4b levels and increased humoral immune and autoantibody responses. A recently published abstract identified on PubMed highlights a number of these changes. Jyonouchi et al. compared responses of peripheral blood mononuclear cells to a mitogen (lipopolysaccharide) and antigens (tetanus toxoid, house dust mite) and reported an excessive innate immune response and a disruption of the regulatory cytokines. It should be noted that these do not appear to be consistent findings. Furthermore, the immunological differences between children with ASDs and controls that have been reported are often small, with values lying close to the normal range for children. To date there is not a clear pattern of immunological abnormalities in ASDs, with various abnormalities being reported in a proportion of children. There is no convincing evidence as to a causal relationship between defects of the immune system and ASDs.

154. A number of reports from the “grey literature” were brought to the attention of the MRC Autism Review, which claimed that pro-inflammatory cytokines may be elevated in the serum of individuals with ASDs. This finding, if true, could have wide-ranging effects including the possibility of altering the endothelium of cerebral blood vessels. The lack of fever, cachexia and evidence of substantial inflammation (apart from the mild inflammatory infiltrate in the intestine) makes it unlikely that pro-inflammatory cytokines are persistently elevated. This remains to be determined, but could be achieved relatively easily through performing ELISA tests, in conjunction with the use of appropriate controls.

**Suggested Physical Abnormalities**

155. There are no known physical markers of ASDs. ASDs can co-occur with other conditions, but there is some debate as to the frequency of associated medical problems. Research on brain abnormalities has been hampered by the small number of brain samples available for study. Current evidence suggests many people with ASDs may have larger, heavier brains, with cellular abnormalities in a number of regions – but no large lesion has been found to be specific or universal in ASDs. Advances in functional brain imaging may improve understanding of the brain basis of ASDs – studies to date have found under-activation in areas associated with planning and control of complex action, and in areas associated with processing socio-emotional information.

156. In general ASDs have not been thought to be associated with physical anomalies. However, there are methodological challenges to the assessment of possible associations, including the need for large samples in order to reliably identify malformations which are themselves relatively rare (for example sensorineural hearing loss, 1-2 per 1000 live births). As with ASDs the prevalence of these conditions is most reliably estimated by using careful methods of ascertainment and diagnosis.
A further issue is that most studies have identified the prevalence of such abnormalities in those with a diagnosis of ASD, i.e. estimated the odds of having a structural malformation given a diagnosis of ASD. However to estimate the risk of developing ASD given the presence of a certain condition or structural abnormality requires a cross sectional study of the affected, e.g. those with congenital malformations, to determine risk of ASD in these groups. This has not been performed. In theory, if such associations were found, they might give clues to stages of prenatal development when key factors operate to cause ASDs. Similarly, differences in brain structures formed before birth (see below) may be informative regarding timing of abnormalities in development, and help to narrow the range of possible environmental factors.

‘What is the co-morbidity of ASDs spectrum disorders with other medical conditions?’

This question is best addressed by population-based investigations in which identifiable medical conditions have been found in association with cases of ASDs that meet conventional criteria for diagnosis. Whether the two conditions are coincidental, or whether the medical condition associated with ASDs plays some causal or permissive role in its manifestation, cannot of course be answered by such an investigation.

Criteria for identification of comorbidity include:
- systematic information about the medical condition
- conventional definition of ASDs
- population defined by age range
- independent verification of medical and psychiatric diagnoses

It is worth noting that there is considerable controversy in the published literature about the degree of comorbidity. There are those who believe the ‘true’ rate of medical conditions in a representative series of children with ASDs is about a third\(^2\), and those who take the view the figure is much lower, at around 10%. According to the proponents of the higher figure, the argument runs, if sufficiently intensive investigations are done, hidden medical conditions will be uncovered. A recent review of epidemiological studies that had examined the prevalence of a wide range of medical conditions\(^4\) reported a consensus mean figure of about 6% (median almost identical). This is unlikely to end the debate, as the quality of the studies reviewed, and the intensity with which hidden medical pathology was investigated, was very variable.

Comorbid medical conditions included epilepsy, cerebral palsy, fragile X, tuberous sclerosis, sensory impairments of hearing and vision, Down’s syndrome, neurofibromatosis, congenital rubella and phenylketonuria. Epilepsy and cerebral palsy were the most prevalent. Gillberg reports that external ear anomalies have been observed more frequently in some studies of ASDs\(^5\). Increased prevalence of autistic symptomatology - but not ASDs per se - has been reported among congenitally blind and deaf children. Median figures of 3.1% for cases of ASDs associated with hearing impairments and 1.3% for visual impairments has been found in a review of epidemiological studies in which these data were available\(^6\). In a longitudinal clinic based study of children with hearing impairment (cited on page 94 in reference\(^3\)), Rapin found that 5% had ASD. However this estimate may be higher reflecting selection biases in a clinic rather than general population sample. Researchers have suggested that sensory disabilities may limit the child’s access to social communication, and hence cause at least transient difficulties in social understanding that resemble to some extent the more profound and persistent social deficits seen in ASDs\(^6\).
Brain Abnormalities

Structural studies

162. Although ASD was eventually recognised as a disorder of brain functioning in the 1960s, our understanding of the underlying mechanisms has been slow to develop. Any adequate neurobiological model of ASDs has to account for the sex ratio; the association with mental retardation, epilepsy and EEG abnormalities; the age of onset and regression in some affected individuals, as well as the specific symptomatology. A major practical obstacle has been a dearth of tissue from the brains of people with ASDs who have died, so that qualitative findings from a relatively small number of individuals have had a disproportionate influence on explanatory models. To date, there have been two major studies\(^206,207\). Each has reported some specific findings not yet replicated elsewhere, but areas of agreement include:

- brain weight is increased in an as yet uncertain proportion of individuals with ASDs;
- decreased Purkinje cell number is seen in the majority of (but not all) cases;
- developmental abnormalities of the inferior olive are a common observation.

163. There is convergent evidence for these findings. A number of structural imaging studies \textit{in vivo} have now reported increased brain volume in children and adults with ASDs, using magnetic resonance imaging (MRI)\(^208-215\). Similarly head circumference is increased in a proportion of individuals\(^216-220\). The MRI and head circumference changes are apparent from about 3-4 years of age. There is some preliminary evidence for a disproportion in the grey matter to white matter ratio and also some suggestion of regional variability in increased brain volume. At present, however, there are too few studies to draw definite conclusions. There is some debate as to the mechanisms underlying these increases in brain weight and volume. Thus it is unclear whether the underlying abnormality is overproduction of cells, which subsequently do not undergo selective cell death, or whether the primary problem is a failure of synaptic pruning. Increased head circumference is also seen in a proportion of relatives.

164. With respect to decreased Purkinje cell number, in some individuals with epilepsy this is associated with increased Bergmann glia, suggesting that some loss may be secondary to seizures. Nevertheless the presence of other developmental cerebellar abnormalities suggests that decreased Purkinje cell number probably occurs late in the prenatal period or early in postnatal development. Although there are claims of specific hypoplasia of cerebellar vermal lobules VI and VII\(^221,222\), there is no convincing replication of these findings outside Courchesne’s laboratory; neither is there evidence for more widespread cerebellar hypoplasia. Developmental abnormalities of the inferior olive seldom occur in isolation, nearly always being found in association with regions of cortical maldevelopment. There is also agreement between studies that some of the observed neuropathology has a prenatal onset. A hypoplastic facial nucleus in one individual has, with other evidence, led to an estimation of onset of abnormal development at 4 weeks gestation; olivary abnormalities suggest that some abnormal mechanisms are operating by 12 weeks gestation, whereas cerebellar abnormalities have been interpreted as suggesting an onset by about 32 weeks gestation.

165. Further evidence and replication of findings is needed in this area. Animal models may be useful – not to model ASDs per se (which involve peculiarly human functions such as imagination and social insight), but perhaps to explore specific aspects of behaviour (e.g. repetitive behaviour, stereotypies), and elucidate connections between key brain regions. Animal models may also be
used to test hypotheses about possible physiological abnormalities and their effects on the brain. Potentially, structural abnormalities may inform genetic studies, clarify which environmental hypotheses are biologically plausible, and help identify the stage of development at which the causes of ASDs operate.

**Functional abnormalities**

166. New technologies have allowed imaging of the brain in action, using for example positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Studies to date reveal areas of relatively low activity (hypometabolism) in the cerebral cortex, but there is little agreement as to which areas of the brain are specifically affected. Recent fMRI studies have noted abnormal localisation of activity associated with diverse cognitive tasks. A common finding, though one not specific to ASDs, is reduced activation of the frontal lobes—thought to be crucial areas for the control of complex behaviour (planning, and so forth; see below in relation to psychological theories). There may also be abnormalities in the limbic system, involved in processing of socio-emotional information. Taken together with the EEG findings and the association with epilepsy, it appears that ASD is associated with abnormal cortical organisation, although the extent to which this a localised versus generalised phenomena is currently unclear.

**Neurochemistry**

167. Over the years virtually every neurotransmitter system has been implicated in the pathogenesis of ASDs. The links have usually been based upon similarities between autistic behaviours and the consequences of drug administration in animals and man. It is widely recognised, however, that although current drug treatments can improve some behavioural abnormalities in ASDs, the core symptomatology is relatively resistant to successful pharmacological intervention and that drug actions may be relatively non-specific. The role of neurotransmitters in brain development is also appreciated, although difficult to investigate directly in ASDs. Recently there has been increasing interest in neurochemical studies using donated tissue and the investigation of neurotransmitter systems using radioisotope techniques.

168. Many claims of abnormalities in neurotransmitter systems have either not replicated or are internally inconsistent. An elevation in blood serotonin is a relatively consistent finding in the field (for a review see, although see Croonenberghs et al. for a more complex investigation) and appears to reflect increased storage in platelets rather than abnormal synthesis. Some studies have also observed hyperserotonemia in relatives. Claims of an association between ASDs and a particular variant of the serotonin transporter gene have so far not been replicated and there is no association between serotonin levels and behaviour in individuals with ASDs. Metabolites of serotonin in the CSF are unremarkable and neither genetic nor post-mortem studies have found evidence of receptor abnormalities. A recent positron emission tomography (PET) imaging study has demonstrated that the normal pattern of high brain serotonin synthesis capacity in childhood may be disrupted in ASDs, but it is unclear whether this finding is connected to unusual levels of platelet serotonin or is secondary to abnormal brain development.

169. Results of studies of the dopaminergic and noradrenaline systems are contradictory. There is no evidence of a consistent elevation of dopamine or its metabolites in plasma or urine, nor of noradrenaline, although it has been suggested that the sympathetic nervous system might be hyper-responsive to stress. There are very recent studies of the cholinergic and GABAergic systems.
Many neurotransmitter systems have been proposed as being involved in ASDs, but there is little supportive evidence.

170. In summary, further investigation of the relationship between brain serotonin synthesis and other indices of serotonergic function appears warranted. There is also scope for further post-mortem work examining the role of the GABAergic and glutaminergic systems, as both neurotransmitters have been implicated in the pathogenesis of epilepsy. Future studies will need to utilise IQ matched controls to determine which abnormalities are specific to ASDs as well as genetically sensitive designs. The possibility that genes may act through effects on the intrauterine environment also merits further investigation.

**Epilepsy**

171. The association between idiopathic ASDs and epilepsy has been recognised since the late 1960's and seizures are a significant cause of morbidity and mortality for individuals with ASDs. Estimates of the proportion of individuals affected vary, but by adulthood about one third of individuals with ASDs have developed epilepsy. There has been no systematic study of the prevalence of seizures across the entire autism spectrum. In the general population the incidence of seizures falls rapidly from a peak in the first year, only rising again much later in life. By contrast in ASDs there is a bimodal distribution in the age of onset, with the childhood peak followed by a rise in incidence in adolescence and early adult life. There is no indication that idiopathic ASDs are associated with any particular seizure type (although there is a strong association between tuberous sclerosis and infantile spasms), nor with a preferential location for seizure foci. Between 15 and 36% of children with ASDs but without epilepsy show EEG abnormalities; these are identified more frequently if EEG's are repeated or if magnetoencephalography is used, as this is more sensitive than EEG. There is no consistent evidence for a characteristic EEG pattern.

172. What underlies the association with epilepsy and EEG abnormalities? Although there is a strong genetic contribution to idiopathic ASDs, the link between genes and seizures appears to be mediated by abnormal brain development, as the rate of seizures does not appear to be elevated amongst relatives. There is no evidence from post-mortem or neuroimaging studies that epilepsy arises on the basis of hippocampal sclerosis. One study of ASDs has reported evidence of cortical dysgenesis in individuals with epilepsy, PET and SPECT studies reveal areas of focal cortical hypometabolism (reviewed by Ryu et al.). Abnormal cortical development has also been identified in the small number of children with ASDs who have come to surgery for medically intractable seizures.

173. Recently there has been particular interest in the relationship between epileptiform activity and autistic regression. Autistic regression most typically occurs during the second year of life. Although estimates vary, perhaps 25% to 33% of children with ASDs lose speech sometimes associated with loss of social skills. Usually speech has not progressed beyond single words before loss and regression is much more common amongst children with ASDs than those with specific language disorder. The relationship between autistic regression and abnormal brain activity is controversial. There is general agreement that in the majority of children who regress there is no association with clinical seizures. Nevertheless the observation that possibly 15-20% of children...
with ASDs without seizures have an epileptiform EEG has raised the possibility of subclinical seizures, and parallels have been drawn with Landau Kleffner syndrome (an acquired aphasia usually associated with a characteristic pattern of EEG abnormality and seizures).

Epileptiform EEG’s seem to be more common amongst children without seizures who regress than those who do not regress, but the possibility that these findings are simply a marker of more abnormal brain development is widely recognised. At present the only indication for neurosurgical intervention in ASDs is for the treatment of medically intractable epilepsy. In terms of future research it will be important to establish if there are any specific genetic or environmental risk factors associated with the development of epilepsy in individuals on the autism spectrum and to more clearly establish the relationship between EEG abnormalities, underlying brain dysfunction and autistic regression.

Suggested Psychological Abnormalities

It is important to know not only what is different in the brains and behaviour of people with ASDs, but also what is special about how they perceive and understand the world. There are three main psychological theories of ASDs at present, focusing on social understanding, control of behaviour, and detail-focus. The specificity, universality and primacy of the postulated psychological differences have yet to be established. The implications for biological investigation and practical intervention have begun to be explored (particularly for social deficit theories), but further work is needed.

Abnormalities in brain structure or function have their effect on behaviour through abnormal development of psychological functions. Several psychological theories attempt to explain the nature of specific symptoms in ASDs; three are briefly reviewed below. In principle, a full psychological understanding of ASDs could inform both studies of the neurobiological basis and educational approaches. Psychological theories drive functional brain imaging studies, and investigation of possible parallels with acquired brain injury, which may elucidate the brain pathways affected in ASDs. Educational approaches have taken some direction from psychological accounts, but further work is needed to build effective bridges from theory to practice.

The Theory of Mind Deficit Theory (ToM)

This theory has been successful in suggesting a cause of the core social and communicative impairments in ASDs (see Baron-Cohen et al. for review). Theory of mind refers to the everyday ability to attribute mental states (beliefs, desires) in order to understand and predict behaviour. People with ASDs appear to be specifically impaired in this ability, as reflected in tests of mental state attribution. The ability to ‘know what someone is thinking’ as assessed in these tests, is related to everyday social and communicative competence. Some diagnostic specificity has been demonstrated (e.g., against Gilles de la Tourette Syndrome, Down’s Syndrome), but these studies need to be extended to other conditions.

The neural basis of ‘Theory of mind’ has been explored through neuropsychological and brain imaging studies. A number of studies of ToM following acquired brain damage (e.g. stroke) suggest an association between orbito- and medial-frontal cortex, and amygdala pathology and ToM deficits. Functional imaging studies (PET and fMRI) have highlighted similar areas and have pinpointed reduced activation in medial-frontal cortex, temporal poles and superior temporal sulcus. These candidate areas will be of interest in identifying the action of specific genetic or environmental factors on brain development.
The ToM deficit theory has also had practical implications. Attempts have been made to remediate ToM skills at the primary school level, with some success but limited generalisation. Deficits in ToM and emotion recognition at later ages are the focus for current attempts at computerized instruction (e.g. CD-ROM developed by Cambridge Autism Research Centre/Shirley Foundation Project). Deficits in social perception deficits may be the earliest reliable signs of ASD.

The Executive Function Theory (EF)

This theory postulates deficits in those abilities thought to depend on the frontal lobes that allow flexible behaviour. ‘Executive function’ is a term covering a range of high-level abilities such as planning future action, modifying behaviour according to feedback, shifting between different behaviours, resisting habitual but no longer adaptive behaviours. People with ASDs have been shown to perform poorly on tests of many of these functions (work reviewed in Russell). It has been suggested that deficits in EF can explain some of the rigid and perseverative behaviour seen in ASDs, and may account for the difficulty of even some very high-functioning individuals with ASDs to manage the practicalities of everyday life. Patients with acquired frontal lobe damage (e.g. from head injury) show similar difficulties on EF tests and in everyday planning and decision-making.

There are many neurological studies of EF outside ASDs. Studies of acquired brain damage suggest dorsolateral prefrontal cortex and fronto-striatal/cerebellar pathology associated with EF deficits. The brain basis of EFs is also likely to involve connections of these areas with other systems such as basal ganglia, striatum and cerebellum.

Although EF deficits have been documented in many individuals with ASDs (e.g. they have not always been found in those of truly normal IQ) EF deficits may be therefore be a common, but not necessary, feature of ASD. Equally, there does not seem to yet be a consensus on which aspect of EF is typical of ASDs (some studies find it is in planning, others find it is in inhibition, others in following arbitrary rules, etc). Finally, EF deficits are far from specific to ASDs, and appear in many clinical conditions (e.g. ADHD, conduct disorder). This may in the long run limit their potential as diagnostic markers. However, remediation of these difficulties could, in principle, potentially improve the independent living skills of adults with ASDs.

Treatments are currently available that address planning difficulties. Many schools for children with ASDs are addressing EF deficits by using explicit structuring of activities in a cookbook approach to daily-life skills. In addition, pharmacological treatments can be targeted at stereotypies and obsessive phenomena (see page 50).

The Central Coherence Theory (CC)

This theory and one of its variants, the theory of enhanced perceptual discrimination, attempt to explain the uneven profile of abilities and difficulties in ASDs. Central coherence refers to the everyday tendency to put information together to extract higher-level meaning, to remember, for example, the gist of a story rather than its details or exact words. People with ASDs seem to show a bias, instead, for part over wholes – and often excel at noticing and recalling detailed information (referred to as ‘weak coherence’). Perception and processing of features is believed to be superior, possibly at the expense of processing global information (currently debated).
185. Weak CC appears to date to characterise people with ASDs at both high and low-functioning ends of the spectrum (see review by Happé265). However, we do not yet know if these tests have diagnostic specificity – that is, whether other groups also show a detail-focused processing style. Weak CC with normal or superior intelligence has been found in fathers of boys with ASDs80,266, suggesting that this feature could be part of the broader phenotype.

186. The brain basis of this processing bias has not yet been explored, with the exception of one brain imaging study226, and the implications of this theory for educational intervention have not been investigated.

187. It is as yet unclear how theory of mind deficits, problems in executive functions and the tendency for weak coherence relate – whether all three describe different aspects of ASD, or whether one constitutes the primary core difficulty from which the others arise. Practical challenges for addressing such issues include the difficulty of studying the very early development of children with ASDs, given later diagnosis. It remains to be seen which psychological deficits/biases emerge first in development of ASDs, and which aspects represent secondary effects.

188. Despite extensive research on psychological theories of ASDs, there remains fairly little understanding of the frequency or significance of the sensory abnormalities often highlighted in parental and autobiographical accounts. Nor is the association of ASDs with general intellectual disability well understood. A recent population study28 suggests that instead of the risk of low IQ in ASDs being 75% (the traditional figure11) it may be much lower (only 25%). The possible developmental ‘knock-on’ effects of e.g. lack theory of mind, for learning through social attention, may be important for language267,268 and for general intelligence269 – and have implications for remediation.

Factors that influence the severity and course

189. More information is needed regarding the long-term outcome and life course of people with ASDs. Depression and anxiety are common associated problems, and sleep disorders are frequently reported. The crucial topic of intervention lay outside the scope of the present review, but good educational approaches exist, and there is a need for more systematic research to demonstrate efficacy. Drugs currently administered target associated difficulties (e.g. anxiety, hyperactivity) only, and careful monitoring of side effects is vital for individuals with ASD for whom communication is a key difficulty.

190. There are few longitudinal studies following individuals ascertained from population-based studies to adolescence and adult life. Those that are available have tended to come from earlier studies of identified ‘classical’ ASDs. In the studies cited by Gillberg270 a good outcome, normal or near normal social life and acceptable functioning at work or school was reported in 5-17% of individuals. In other studies the single best predictor of outcome is IQ22,23 – both cited in Gillberg270. In a more recent review of studies reporting longitudinal follow up data in ASDs271, 21 studies were identified, of variable quality, reporting outcome at an average age of 24 years. From these studies, the authors concluded that young adults with ASDs may have continued problems with personal communication and social interaction but may, depending on intellectual level, function acceptably at work. There was also some suggestion that the mortality rate may be higher for individuals with an ASD. However the quality of these data are such that no firm conclusions can be drawn.
191. Making an accurate psychiatric diagnosis in people with ASDs has inherent difficulties: impoverished language, literal interpretation of questions, concrete thinking, impaired general ability, and obsessionality, rigidly pursued interests and bizarre preoccupations, that may be difficult to distinguish from delusional and paranoid thoughts. Furthermore, many individuals have no speech or so little that they cannot express their feelings in any way.

192. Many case reports exist of psychiatric disorder in ASDs but there are no epidemiological studies. Hence the prevalence of these difficulties is unknown. Estimates of relative prevalence suggest that depression is associated with ASDs most often, followed by anxiety disorder. The risk for depression in adolescence and adulthood must be considered high, estimated as between 4.4% and 57.6%.

193. Larger scale studies have not found evidence of increased rates of schizophrenia in ASDs, although cases exist. Catatonia has been found as a later complication superimposed on ASDs by one study, where 17% of referrals in a clinic sample of 506 individuals were affected. Cases of comorbidity with compulsive behaviours, hyperactivity, tics and Tourette's syndrome have also been described.

194. For the purpose of this report Howlin compiled all available published reports and reviews of psychiatric disturbance in ASDs between 1951 and 2001. A total of 189 individuals were identified from 32 reports, which included only individuals with a clear diagnosis above childhood age. This review found depression present in 39% of cases reported, anxiety disorders in 17%, mania and bipolar disorders in 10%, schizophrenia in 7%, and isolated psychotic symptoms in another 7%. There were few differences when the individuals were divided into those diagnosed with ASDs and those with Asperger syndrome or high-functioning ASDs, but depressive symptoms and symptoms of anxiety were more frequent in the Asperger group.

195. Children with ASDs, like children with other forms of developmental disorder, are at particular risk for sleep disorders. Problems include night-time settling difficulties, night waking, duration of nighttime sleep, sleep onset, early waking. Children with ASDs may have higher rates of sleep problems than children with intellectual impairment alone, and these problems appear to occur at all levels of intellectual functioning.

196. There is evidence for abnormalities in both rapid eye movement (REM) and non-REM sleep in children with mental retardation. A number of physiological abnormalities of REM sleep have been found in children with ASDs, such as: latency, density, and immaturity. NREM sleep may also be abnormal.
197. Associations between sleep abnormalities and behavioural disturbances (such as challenging behaviour) have been observed in children with ASDs\textsuperscript{298}, Down’s syndrome\textsuperscript{302}, epilepsy\textsuperscript{303}, mental retardation\textsuperscript{292}, and tuberous sclerosis\textsuperscript{304}. Sleep deprivation or dysfunction has been associated with poor performance on a variety of cognitive tasks, for example, concentration, digit span, and executive functions\textsuperscript{305-307}. A number of studies have suggested the importance of REM sleep in memory formation of different types\textsuperscript{310-314}. The role of sleep difficulties in deficits in such processes is as yet unclear.

**Intervention**

198. The scope and remit of the present review did not allow a focus on intervention, and this important topic is the subject of other recent reports or projects underway (see Journal of Autism and Developmental Disorders 2000, 30(5) for recent collection of articles on Interventions and Future Directions for Research). Howlin\textsuperscript{272} has reviewed 50 years of behavioural and pharmacological treatment approaches for ASD. The New York Health Department also provided a very detailed and comprehensive review in 2000\textsuperscript{315}. Both reviews highlight the importance of educational and social-community support, and the benefit of structured educational regimes. The use of tried behavioural and educational programmes in young children was recommended. Studies show that meaningful gains can be obtained and that a child’s rate of progress can be improved by a combination of educational, developmental or behavioural treatments\textsuperscript{316}. Intensive home-based programmes have been most systematically evaluated, but numbers are small and no randomised control trials have been performed\textsuperscript{317}. Current studies\textsuperscript{318} have been more cautious in their conclusions than the original reports\textsuperscript{319}. In evaluation studies of behavioural approaches it is not possible to identify which components in these programmes are most effective \textsuperscript{320, 321}. Other less intensive behavioural approaches are equally effective.

199. Psychopharmacological treatments in use at present do not treat the core features of ASD. Indeed, in the absence of good understanding of the brain basis of ASDs, there is no rationale for any pharmacological treatment of ASD specifically, although a wide range of psychopharmacological agents has been employed. These have generally been given to ameliorate associated symptomatology, including: poor attention and concentration, obsessive phenomena, compulsions or rituals, stereotyped behaviours, excessive anxiety, depressed mood, sleep problems and self injury. They include drugs influencing serotonergic function (5-HT reuptake inhibitors), which may reduce repetitive behaviour and aggression\textsuperscript{322,323}, but see\textsuperscript{324,325}; drugs that inhibit impulse transmission in dopaminergic neurons, which may reduce challenging behaviours\textsuperscript{326,327}; drugs influencing adrenaline and noradrenaline systems to reduce overactivity\textsuperscript{328-330}; and drugs with multiple actions on neurotransmitter systems. There is concern among parents and others working with people with ASDs that pharmacological treatments may be used in place of more appropriate behavioural and educational approaches, particularly with adults in residential care. For individuals with limited communication, monitoring of possible side-effects is particularly important in any treatment and especially in drug treatments with known risks.
6. TAKING FORWARD RESEARCH INTO AUTISM SPECTRUM DISORDERS

Introduction

200. In considering the way forward for research on autism spectrum disorders (ASDs), we have focused on the following strategic themes, which are reflected in the headings used in the remainder of this section.

• Researching and refining case definition
• Developing the epidemiological framework
• Enhancing integrated research strategies
• Developing hypotheses about abnormal physiology
• Strengthening research capacity and the interface with services
• Adding value through lay participation
• Taking the next steps

201. We have not presumed to provide a detailed plan for the science. Nor have we set out a menu of the many research projects that might merit support, not least because earlier sections of this report deal with opportunities and gaps in considerable detail. This “way forward” takes account of the strengths and gaps in autism research, both within the UK and internationally, some of the key scientific opportunities, and the need to enhance the infrastructure – particularly at the research-service interface. We have been mindful throughout of the importance of the existing framework of guidance and approval systems for ethics in research, in particular the need to consider the ability of individual people with autism spectrum disorders to give or withhold their consent.

Researching and Refining Case Definition

202. Improved definition of the outward characteristics (phenotypes) of the subgroups within the spectrum, and overlaps with other conditions, will underpin research on causes and mechanisms. Accuracy and consistency of case definition and diagnosis is a crucial issue both for services and for research. Improvements will help researchers compare different studies with each other and across time. Further research is needed to develop and evaluate the tools for case definition.

203. The definition of autism spectrum disorders is fundamental when addressing questions of their assessment, frequency, causes, outcomes and management. The development and validation of instruments for use in research and in services is an area in which the UK has strengths and continues to be a key area for research.

204. Consistency between studies and over time are crucial issues that can significantly affect interpretation of research findings. This is well illustrated by current difficulties in confidently answering the question “Has autism increased over recent years?” Fortunately, new research is able to build on the consensus achieved around the diagnostic triad and the recent development of systematic assessment tools (see Chapter 3).
While our focus is on research, there is clearly overlap with the need for definitions that have utility in the clinical and service context. For this reason a continuing dialogue between research targeting fundamental questions and that aimed at developing and evaluating tools for services is essential.

There is consensus on the broad criteria used to identify those with autism spectrum disorders. However, questions remain about the interpretation of more subtle patterns. This requires detailed information on patterns of impairment within population and family studies.

Further work is required to develop and test the classification of subgroups within pervasive developmental disorders. For instance, do children with autism spectrum disorders who show apparent regression represent a meaningful subgroup?

Further work is needed to develop reliable methods to assist researchers in mapping identified impairments onto the currently recognised diagnostic categories.

Developmental disorders by their very nature change with increasing age, yet many of the instruments may be specific for a relatively narrow age range. To understand the evolution of phenotype with increasing age there is a need to improve ascertainment of autism spectrum disorders in the very young, adolescents and adults.

An important question is the extent to which the phenotypic and genetic features of autism spectrum disorders overlap with those of other developmental disorders, such as specific language disorders, obsessive-compulsive disorders and attention-deficit hyperactivity.

Developing the Epidemiological Framework

Epidemiology has a central role in addressing questions about prevalence, incidence and their relation to time, place and person within populations. It is key in the formal testing of causal hypotheses, specifically in working out the contributions of environment and genetic influences. Such a framework is also necessary for research on case definition, co-morbidity, natural history and outcome.

Population-based studies that identify affected children or adults using active ascertainment and common diagnostic criteria have several advantages, including the provision of adequate numbers of affected individuals, identified using a common methodology, to test important hypotheses about causes and to provide unbiased estimates of outcome.

Recent epidemiological studies within the UK confirm earlier and, at the time, relatively controversial observations that autism spectrum disorders are among the most common developmental disorders of childhood. A particular strength of these recent studies is their use of similar definitions and methods of ascertainment. On the other hand they are individually relatively small and so have limited power to address important issues about causes, natural history and outcome, particularly at a sub-group level.

There may be potential for some existing epidemiological studies to be combined to test simple hypotheses, for example relating to the prevalence of gastrointestinal symptoms and other conditions among people with autism spectrum disorders.
215. Considerable advances are being made internationally towards identifying candidate genes for autism spectrum disorders. New, large epidemiological studies that include genetic data would allow these advances to be taken forward fairly rapidly, in the context of a general population sample, to address questions about genes and environment. The scientific rationale for collecting DNA would be strong and should conform to guidelines (e.g. MRC Ethics Series Human Tissue and Biological Samples for Use in Research). The UK is well placed to exploit this approach but such studies are challenging to mount and require strong national - and possibly international - scientific collaboration.

216. In addition, such large studies can contribute well-characterised cohorts for prospective investigation of longer term outcomes. Such a cohort, of affected people ascertained over a relatively short period of time, is likely to be qualitatively different from health service registers developed for needs assessment and health service planning. However, some overlap may exist where researchers work particularly closely with health services.

217. There have been considerable advances internationally towards identifying candidate genes for the autism spectrum disorders – to which UK science is making a significant contribution. While there is excitement about these advances, examples from other areas of biomedicine make it clear that to identify susceptibility loci and determine how they interact is a complex task requiring a substantial, multidisciplinary research effort.

218. Various models for genetic epidemiological studies exist and their appropriateness depends on the questions being addressed. Traditional behavioural genetic designs may be useful for investigating the nature of the relationship of different subtypes of the autism spectrum disorders, specifically the degree to which Asperger’s syndrome and other autism variants are part of a spectrum. These designs are also potentially useful for testing some of the cognitive theories of autism.

219. Another established design already applied in the autism field is the twin study in which, for example, the study of twins with identical genetic backgrounds (“monozygotic” twins) but with differing diagnoses can shed light on environmental risk factors. Further twin studies could also valuably address the issue of whether genetic liability is related to symptom severity.

220. Family studies with a case control design can help both to refine the definition of phenotypes and to examine how particular manifestations are correlated within pairs of affected siblings. For instance, they may be able to help ascertain the extent to which ‘regression’ is a feature within families.

221. Twin and family designs can be complemented by large scale genetic association studies, based on general population samples, focussing on candidate genes. In addition to helping confirm susceptibility genes, whose locations have been mapped in affected multiplex families, they provide a fairly simple and quick means of testing whether the susceptibility genes involved in one putative ASD subtype are also involved in other subtypes.

222. Studies of families with an affected member, such as the ‘Baby Sibs Projects’ in North America (http://www.naar.org/grants/babysibs.pdf), potentially provide an interesting model for exploring events that precede clinical diagnosis and their relationship to later social, behavioural and brain development.
Enhancing Integrated Research Strategies

223. The UK has a long history of internationally cutting edge research on autism spectrum disorders, particularly in developmental psychopathology, behavioural and molecular genetics, neuropathology and assessment. These basic science programmes provide a strong platform on which to build a more integrated approach to defining risk factors and mechanisms, thus laying the basis for new and more effective approaches to diagnosis, treatment and perhaps prevention.

224. An integrated neurosciences approach to working out causal pathways is needed, combining structural, functional, behavioural and genetic approaches. Important strategic issues include the following points.

225. There is currently some uncertainty about the specificity and significance of findings in brains of people with autism spectrum disorders who have died. This is partly due to the limited availability of such brains. More effective collection of tissue from affected individuals and controls is needed, perhaps in collaboration with European researchers. In the USA much has been done by lay organisations to encourage brain donation.

226. Imaging of the living brain, using for example magnetic resonance imaging and positron emission tomography, is a powerful component of an integrated neurosciences strategy. There may be a case for ensuring that structural and functional images of brains can be more readily shared by the research community. Most of the imaging work has involved adult volunteers and the techniques require adaptation for use with children. The selection and availability of appropriate control participants is an important consideration in both neuropathology and imaging studies. Careful collection of diagnostic and psychometric information is crucial.

227. Conceptually, psychology has a pivotal place in interpreting links between brain, mind and behaviour. UK research in cognitive and behavioural psychology has provided many significant insights into the definition and diagnosis of autism spectrum disorders and the key assets and deficits. Much of this work has been based on intensive study of relatively small numbers of people. There are increasing opportunities to test some of the cognitive theories within integrated genetic and epidemiological designs and to tackle fundamental issues such as heterogeneity and the broader set of features of autism spectrum disorders, for example cognitive and language impairment. Such integrated multidisciplinary approaches will allow well substantiated theories to be further tested and refined, both in laboratory and every day settings.

228. New ways forward for practitioners and parents may come not only from work on deficits but also in understanding special skills that occur in autism spectrum disorders. There is considerable scope for investigating brain mechanisms in the context of studies of the efficacy of early interventions. To date these have focused on very basic behaviours but it is possible that intensive teaching of social interaction skills in older and more able individuals could be combined with psychological and imaging investigations.

229. Useful animal models of autism as a condition are not practically possible. However, analysis of particular behavioural symptoms, the relationships between them, and the underlying neuropathology, neurochemistry and neurophysiology, may be susceptible to mouse genetic models combined with a variety of structural and functional studies. This is clearly another area for multidisciplinary collaboration.
Developing Hypotheses about Abnormal Physiology

230. There are a wide range and variety of observations and theories on the suggested role of vaccines, drugs, toxins, infections and diet as suggested risk factors for autism. Many of the studies of diet, intestinal permeability and inflammatory responses in the gastro-intestinal mucosa have come from the UK, but the field is relatively young and fragmented. Greater methodological rigour and independent replication are crucial in much of this work.

231. Many findings in the area of abnormal physiology are not available in the peer reviewed literature, or are not well described, and these preliminary findings need to be confirmed by independent replication in other centres. Currently, the low volume of research and the lack of methodological rigor and independent replication means that many of these claims find little support from the wider scientific community.

232. Nevertheless, many of the observations are interesting and in principle worth investigating. Moreover, potentially modifiable risk factors are attractive targets for interventions. A start might be made by testing such hypotheses in robust but relatively simple research designs, so that the less likely ideas can be put to one side and further effort and investment can focus on the areas that strong preliminary evidence identifies as more likely to be productive.

233. Our review of the evidence highlights the need to take account of the following:

- Gastroenterological studies need to be controlled for bowel habit, eating behaviour and autism spectrum disorder subtypes. Closer collaboration between the different clinical disciplines, in particular gastroenterology and psychiatry, is crucial.
- The plausibility of suggested dietary risk factors, such as casein and gluten, could be tested more systematically through a combination challenge tests and assays of blood metabolites.
- The plausibility of the sulphation and sulphate oxidation theories could be tested through more robust biochemical methods than hitherto. Account also needs to be taken of a broader range of evidence, such as of reported polymorphisms in the relevant metabolic enzymes.
- On current evidence, reports of disturbances in chemical messengers in the brain or immune system are not well substantiated, and may be incidental or secondary effects, rather than causal. The research needs a stronger conceptual and methodological base and greater specificity.
- In all of these, choices of sampling strategy, case-definition, measures and controls are crucial and a multidisciplinary collaborative approach is likely to be essential.
- Findings need be published in high quality, peer reviewed journals, not least so that the methods can be replicated and the findings and hypotheses tested independently by other approaches. Where independent replication and different approaches fail to demonstrate a significant association, the case for further work is likely to be weak even if the particular factor cannot be proven to be of no risk.
• Well substantiated, refined hypotheses can then be tested through a variety of other designs. Some will be amenable to case-control or other epidemiologically and genetically sensitive designs and others to investigation in experimental models.

• The feasibility of addressing even biologically plausible theories will depend on the frequency of the susceptible sub-groups as well as that of the exposures of interest.

**Strengthening Research Capacity and the Interface with Services**

234. Researchers, funders and service providers need to consider how best to achieve strategic, integrated research alliances both to sustain excellence and to develop new areas of enquiry; and to ensure the availability of sufficient and appropriately skilled manpower at the research-service interface. It will be timely during 2002 to bring together the various national reviews of services and research relevant to autism spectrum disorders.

**Strengthening Research Capacity**

235. There may be a need for specific measures to promote multidisciplinary collaboration around shared strategic goals. Such collaboration offers established centres of excellence the kind of new scientific opportunities that are essential if they are to sustain their competitiveness internationally. In relation to emerging or currently fragmented national effort, such collaboration can provide access to crucial partners and expertise.

236. A useful model is that employed by the USA National Institutes for Health in promoting and funding collaboration between established centres of excellence in autism research. The NIH experience is that considerable added value is derived from co-ordinating tests and measures, and from sharing data-sets, tissues and other key resources. Such networks are also better placed to support underpinning methodological development, for example to refine case definition and phenotypes, and to provide an attractive training environment.

237. We are conscious of the need to attract young researchers, from both basic scientific as well as clinical disciplines, to this field. There is, however, a research capacity issue in relation to community paediatrics and child psychiatry, both of which subspecialties currently produce relatively few individuals committed to a research career.

238. Basic and applied research in neurodevelopmental disorders has historically played only a small part in medical education. Current exciting advances in our understanding of the molecular and systems basis of brain functioning provide an opportunity for bringing together teaching, research and practice.

239. Similarly, there is a need to strengthen the scientific expertise in relation to the epidemiological study of neurodevelopmental disorders more generally.

240. UK research on gastroenterological symptoms, their significance and management is currently focused on very few academic departments. It would be helpful to engage the gastroenterological research community more widely while at the same time strengthening links to other disciplines.
241. The kind of large-scale prospective epidemiological and genetic studies we have advocated earlier in this section will require additional trained and motivated medical and clinical psychology researchers to be based in a number of UK centres that combine service and research. Not all centres in such a network would necessarily need to include expertise in genetics, epidemiology and imaging, which could be accessed through strategic alliances with those that did.

Nurturing the Research – Service Interface

242. The links between research and services need to be strong in order to recruit and gain access to participants and so that children identified through research can be given appropriate ongoing care and support. Consequently, much research needs to work through service providers (schools, clinics, parent organisations). In this respect, having the National Health Service provides the UK with significant opportunities. It is also important to think beyond autism spectrum disorders. Other disabilities, such as learning and language difficulties, and sensory and motor impairments, are of practical importance to the same teachers, parents and service providers who also work with people with autism spectrum disorders.

243. Service provision for affected individuals and their families is the subject of two separate reviews - The National Initiative on Autism: Screening and Assessment (NIASA) and the National Needs Assessment for autism in Scotland. We would hope that any proposals arising from these reviews will take into account training for research. For example, multicentre epidemiological studies require support from trained professionals in the NHS. While a number of UK centres provide professional training for the assessment and diagnosis of autism spectrum disorders for researchers and clinicians, this is not centrally co-ordinated and there is a substantial waiting list.

244. It is important to co-ordinate research agendas for autism with other national initiatives, such as the National Service Framework for Children.

Adding Value Through Lay Participation

245. The participation in this review of affected individuals and their carers and lay people with experience of patient support and advocacy groups has enriched both the process and outputs. However, they have indicated that there are also broader issues, which, although outside the terms of reference of this review, are important and to which research could make a significant contribution. The effectiveness of interventions, the extent of service needs, and the organisation and delivery of services across health, social services and education are such themes.

246. The partnership developed during the course of this review represents an important milestone in autism research in the UK. Further partnerships are likely to be of benefit by providing researchers and funders with access to user perspectives and lay organisations with access to scientific expertise. Specifically, aspects of patient and carer experience can help scientists better frame their research questions and to work towards outcomes that are more relevant to the intended beneficiaries.
Next Steps

247. Much of the basic research on causes is essentially long term and programmatic in nature. New and important findings will emerge from the current UK and international effort and investment in high quality research, and these too will inform longer term research and funding strategies. Nevertheless there are several achievable steps that could be taken in the near future to enhance services and research for autism spectrum disorders:

• Bring to the attention of policy makers in UK health, social care and education, and to practitioners, researchers and lay audiences the results of the various national reviews relevant to autism spectrum disorders in a co-ordinated way to maximise the sharing of agendas and concerted actions. The kinds of issue that are likely to merit a co-ordinated approach include training for services and research, and how best to ensure that the research and development environment in clinical, social care and educational settings is strong.

• Consider whether specific initiatives are required to stimulate collaboration to further exploit UK strengths in the field and to address important questions where research is currently weak and could be strengthened.

• Encourage the research community to develop high quality research proposals for funding that address the key issues for research identified in this report, in particular case-definition; the roles and interplay between genetic and environmental risk factors; causal pathways and mechanisms; and new approaches to treatment and perhaps prevention.

• Build on the researcher–lay–funder partnership that was indispensable to this review, extending it beyond biomedicine and research, so as to ensure that the best evidence is easily available to all and to facilitate the growth of consumer involvement in the design, conduct and dissemination of research - as a means to enhancing its quality and relevance.
REFERENCES


## LIST OF APPENDICES

<table>
<thead>
<tr>
<th>Appendix 1 Annex 1</th>
<th>Process of the Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix 1 Annex 2</td>
<td>Criteria for Selection and Managing Conflicts of Interest</td>
</tr>
<tr>
<td>Appendix 1 Annex 3</td>
<td>Membership of Review with Declaration Summary</td>
</tr>
<tr>
<td>Appendix 1 Annex 4</td>
<td>Terms of Reference</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>List of Submitted and Suggested Information</td>
</tr>
<tr>
<td>Appendix 3</td>
<td>List of Individuals Specifically Approached</td>
</tr>
<tr>
<td>Appendix 4 Annex 1</td>
<td>Programme 11 July 2001 Workshop</td>
</tr>
<tr>
<td>Appendix 4 Annex 2</td>
<td>Programme 26 September 2001 Workshop</td>
</tr>
<tr>
<td>Appendix 4 Annex 3</td>
<td>Programme 5 November 2001 Workshop</td>
</tr>
<tr>
<td>Appendix 4 Annex 4</td>
<td>Programme for Lay Group Research Methodology Training Day</td>
</tr>
<tr>
<td>Appendix 5</td>
<td>Lay Group Questions</td>
</tr>
</tbody>
</table>
APPENDIX 1 ANNEX 1

Process of the Review

The Review was chaired by Professor Eve Johnstone (Chair, MRC Neurosciences and Mental Health Board and member of MRC Council). The Secretariat was provided by MRC Head Office, with Dr Francesca Happé (Institute of Psychiatry) acting as the Scientific Editorial Consultant for the writing of the Report.

Organisation

The Review was organised into 4 subgroups: three Expert Groups focussed on the following broad scientific areas –

• Epidemiology and Case Definition, chaired by Dr Carol Dezateux
• Psychology and Behaviour, chaired by Professor Uta Frith
• Physiology and Infections, chaired by Professor Derek Jewell

The fourth Group comprised individuals drawn from the Autism community and the MRC Consumer Liaison Group.

The membership of the Expert Groups was agreed by the Review Chairman on the advice of the MRC Head Office secretariat, following consultation with the Group Chairmen; the selection of experts was made following certain criteria (see Appendix 1 Annex 2). Each Expert Group also included 2 members of the Lay Group as observers. All members of the Review were asked for declarations of interest, which were recorded and made available if requested. The membership of the Review, and a summary of declarations are given in Appendix 1 Annex 3. The terms of reference for the Review is given in Appendix 1 Annex 4.

The process of the Review was overseen by a Review Steering Group, which comprised the Chairman, the chairs of the 3 Expert Subgroups, a Lay Group representative, and a representative of the MRC Head Office.

Information

Information considered by the Review came from a number of sources. The Expert Groups used conventional methodologies to retrieve relevant information, including literature searches of peer-reviewed publications on databases such as Medline. Reports published on the Internet were also considered, with particular care being taken to establish their provenance.

The Review also considered information that had not been published in peer-reviewed publications, the so-called “grey literature”. This information came from a number of sources, including suggestions from the Lay Group and their associated networks, and submissions by scientists and lay members of the public (full list of suggested and submitted materials given in Appendix 2). The Lay Group was further responsible for suggesting additional individuals whom the Review could approach directly. The Review invited a number of particular researchers to submit information not yet published in peer-reviewed journals; any evidence was appraised in the same way as peer-reviewed, published literature, where possible (list of individuals approached given in Appendix 3).
Confidentiality of information was managed in the following manner:

- If published, either in print or on the Internet, it was considered as a document in the public domain.
- If in the form of a manuscript accepted for publication, the Expert Groups considered it confidential to the Review Groups, until publication of the paper.
- If a manuscript in preparation or under review, or a specific submission which contained information that the individual submitting considered to be confidential, the Expert Groups considered it confidential to the Review Groups.

**Lay Group Questions**

In addition to providing the Review with alternative information sources, the members of the Lay Group were responsible for identifying a number of questions for the Review to consider. These questions reflected concerns already put forward by parents to the charities represented on the group as well as some issues arising from letters sent directly to the MRC by members of the public. The questions were made available for comment by the various organisations, for example by being posted on a website, with comments and additions were requested. Any subsequent responses were incorporated. Full list of questions at Appendix 5.

**Meetings**

Each of the Expert Groups met 2 or 3 times during the Review process, as well as electronic communication throughout the process. The Lay Group met on several occasions throughout the Review. A Research Methodologies Workshop was arranged for the members of the Lay Group (Programme at Appendix 4 Annex 4).

A larger meeting was held in London on 11 July 2001, with the purpose of a preliminary exploration of the main scientific issues and of the questions presented by the Lay Group, for consideration by the Review. All members of the Review and parties who had expressed an interest were invited to attend. The programme for the meeting is given at Appendix 4 Annex 1.

A synthesis meeting was held in London on 26 September 2001, to which all the members of the Review were invited. The function of the meeting was a discussion of the draft submissions from members of the Expert Groups, for the purpose of bringing together the various themes of the Review, in consideration of the questions presented by the Lay Group. The Programme for the meeting is given in Appendix 4 Annex 2.

A final strategy meeting was held in London on 5 November, to which all members of the Review were invited. In addition, a small number of additional experts were invited, to comment on the draft Report and to advise on the proposed research strategies. The Programme for the meeting is given in Appendix 4 Annex 3.

The Report was drafted by the Secretariat in consultation with the Review Groups. The Steering Group approved the final version.
APPENDIX 1 ANNEX 2

SELECTION OF EXPERTS AND MANAGEMENT OF POTENTIAL CONFLICTS OF INTEREST

The following information was provided to members of the Review Groups by the secretariat as part of information on the code of conduct for members and how to manage potential and perceived conflicts of interest.

Eligibility Criteria for Review Group Members

Scientific Expert Members

The role of the scientific experts is to identify and assess research-based evidence in their field relevant to the terms of reference of the review. They should approach this in a professional manner, i.e. to high standards of accuracy, impartiality and balance, and delivering their contribution to the agreed timescale. They are responsible to the Review Chairman through the Steering Group (of Group chairmen) for the quality of their input. The Groups are collectively responsible for the quality of their contribution to the workshops and final report.

The eligibility criteria for the Experts are as follows:

• Relevant expertise either in autism directly or in the biological or psychological systems, processes and research methodologies relevant to understanding autism.

• Research standing in terms of their breadth and depth of expertise. (This can be assessed through examination of publications, career pathway and recognition within the scientific / medical community or more widely).

• Reputation for objectivity, fairness and balance - being able to stand back from their own research interests; a degree of self-criticism / reflection on their own science / discipline. (For this reason we tend to select experts whom we have seen in action or by consultation with senior research leaders).

• Reputation for being able to work constructively in committee with others – openness to others’ perspectives.

• Their contribution to the overall balance of expertise, experience and gender/geography on the Group.

• Availability and willingness to give of their time.

Lay Members

The role of the Lay Group is (1) to bring a broader perspective to the work of the Groups, e.g. by helping to define the questions and (2) helping to ensure the outcomes of the scientific process are transparent and accessible. This also defines their role as observers on the Groups. As observers, they contribute indirectly to the scientific work of appraising the research and are not directly responsible for the scientific conclusions and recommendations. But in other respects they are members of the Group and should contribute fully to the discussions.
The eligibility criteria for the Lay Group are as follows:

• Experience relevant to the review, as a parent or person with autism, or as a “consumer” of health care and public health more generally.

• Breadth and depth of own experience and of the organisations and networks with which they are associated.

• Objectivity, fairness and balance - being able to stand back from their own specific personal and organisational concerns.

• Ability to work constructively in committee with others – openness to others’ perspectives.

• Their contribution to the overall balance of experience and gender/geography on the Group.

• Availability and willingness to give of their time.

Identifying and Managing “Interests” Relevant to the Autism Review

What Kinds of Interest Should be Declared?

The kinds of interest that should be declared in this review are as follows:

• Connections with other organisations that fund, or lobby for funding, for autism research, including:
  – Specific research priorities of the organisation (e.g. education, environmental exposure, mental health, research on carers); [It may be simplest to register a list of funded projects].
  – A list of members of the scientific advisory committee, or equivalent body, that decides on research priorities and funding.

• MRC funding for research in autism, or plans or actual proposals being developed for such research.

• Employment by MRC, whether as a scientist of administrator.

• Employment by, consultancy for, directorships or shares in a company with an interest in autism.

• Involvement in the MMR litigation, clarifying your role such that it is clear what interest you have in one side or other proving its case. There is a perception that it is important to know whether you or your organisation has been remunerated for advice.
What is the Process for Managing Interests?

All those taking part in the review have been asked to complete declarations of interest. The declarations are not confidential. A tabulated summary of interests will be provided in the papers for meetings of the Groups.

The secretariat seeks clarification when a potential for a conflict of interest is identified either by the person completing the form, the secretariat or the Groups themselves. For instance, we have obtained additional details from those experts and parents who are in some way involved with the class action being brought against manufacturers of the MMR vaccine. The clarifications are available to and discussed by the review Groups.

A Group member may and should declare a previously unrecognised interest to the secretariat or chairman at any time once they recognise there is a potential for conflict (or for a perception by others that there could be a conflict). Members are encouraged to reminding the Group during the course of its business that he or she has a particular interest relevant to a specific item of business. It may be appropriate to absent themselves for that item.
APPENDIX 1 ANNEX 3

Membership of MRC Autism Review

Chairman
Professor Eve Johnstone
University of Edinburgh

Declared Interest
Shareholding in Glaxo-Wellcome
MRC Grant holder (not in autism research)
Member of MRC Council and Neurosciences and Mental Health Board.

Secretariat
Dr. Peter Dukes
MRC Head Office

Employee of MRC

Dr. Chris Watkins
MRC Head Office

Employee of MRC

Mrs Elizabeth Mitchell
MRC Head Office

Employee of MRC

Dr. Francesca Happé
Institute of Psychiatry
(Editorial Consultant – Science)

MRC grant in autism research
Epidemiology Sub Group

Dr. Carol Dezateux (Chair)  
*Institute of Child Health*  
Member of MRC Health Services and Public Health Services Board.  
Colleagues have interest in immunisation policy, including MMR and autism.  
MRC grant holder (unrelated to autism).

Dr. Patrick Bolton  
*University of Cambridge*  
MRC grant and other grants from charitable organisations for autism research.  
Medical advisor to the Tubercous Sclerosis Assoc. and advisor to National Autistic Society.  
Co-Director of Cambridge Autism Research Centre.

Dr. Eric Fombonne  
*McGill University, Canada*  
Consultant for committees/seminars on autism to the Centre For Disease Control (CDC), MIND Institute (California), National Academy of Sciences (Washington DC), the Institute of Molecular Immunisation Safety Review Committee (Washington DC) and the American Academy of Paediatrics.  
MRC grant in autism research.  
Paid consultant to defendants in legal case.

Dr. Stuart Logan  
*Institute of Child Health*  
Consultant in Community Child Health so a clinical interest in immunisation policy.  
Colleagues have specific research interest in immunisation policy, including MMR and autism.

Dr. Lorna Wing  
*National Autistic Society*  
Member & Vice-President of National Autistic Society.  
Part-time consultant to NAS Centre for Social and Communication Disorders.  
Member of Sussex Autistic Society.  
Director of Sussex Autistic Community Trust Ltd.  
Parent of an Autistic Adult.

Mr. Adam Feinstein  
*Lay Observer*

Mr. David Potter  
*Lay Observer*
## Physiology Sub Group

**Professor Derek Jewell (Chair)**  
*University of Oxford*  
Member of MRC Strategy Development Group. Subgroup on research into inflammatory bowel disease and autism.  
MRC Grant holder (unrelated to autism).

**Dr. Anthony Bailey**  
*Institute of Psychiatry*  
MRC employee (MRC Scientist).  
Previous consultant to Ortho Diagnostics (Johnson and Johnson) for a Urinary Peptides study.  
MRC and other grants for autism research.

**Professor Richard Elliott**  
*Institute of Virology, University of Glasgow*  
MRC Grant holder (unrelated to autism).  
Member of MRC Physiological Medicines and Infections Board.

**Dr. Paul Harrison**  
*MRC Institute of Environment and Health, University of Leicester*  
MRC Employee (MRC scientist).

**Dr. Simon Murch**  
*Royal Free Hospital, School of Medicine*  
Collaboration with Dr A. Wakefield and Dr. R. Day in study of gastrointestinal inflammation in autistic children.  
Grants for immunological research in autistic children (not MRC).

**Professor Bert Rima**  
*Queen’s University Belfast*  
MRC grant in Measles virus research and other non-MRC grants.  
Non-commercial grants including a BBSRC grant entitled: Cross-species infection by morbilliviruses.  
Paid consultant to solicitors for defendants in class action.

**Professor Ian Sanderson**  
*London School of Medicine and Dentistry, Queen Mary’s, University of London*  
MRC Grant holder (unrelated to autism research).  
Consultant to solicitors defending legal case. Fees paid into medical school research account.

**Professor Chris Stokes**  
*University of Bristol*  
None.

**Professor Jonathan Rhodes**  
*University of Liverpool*  
MRC and grants from other organisations (unrelated to autism).

**Ms. Rosemary Kessick**  
*Lay Observer*  

**Mr. Jonathan Tommey**  
*Lay Observer*
Psychology Sub Group

Professor Uta Frith (Chair)  
*University College, London*

Member of MRC Strategy Development Group. Subgroup on research into inflammatory bowel disease and autism. 
MRC employee (External Scientific Staff). 
MRC grant in autism research.

Dr. Simon Baron-Cohen  
*University of Cambridge*

Co Director of Cambridge Autism Research Centre. 
MRC and other grants from charitable organisations for autism research.

Professor Jill Boucher  
*University of Warwick*

Number of grants on autism research (not MRC).

Dr. Patricia Howlin  
*St. George’s Hospital Medical School*

Specialist Councillor and member of the ethics committee of the National Autistic Society. 
Funding from a number of organisations on autism research (not the MRC).

Professor Ann Le Couteur  
*University of Newcastle*

Member of International Collaborative Molecular Genetic Study of Autism. 
MRC grant holder for autism research. 
Co-author of Autism Diagnostic Interview - Revised.

Professor Trevor Robbins  
*University of Cambridge*

MRC programme grant holder unrelated to autism; MRC COGG in Brain, behaviour and neuropsychiatry general and indirect relevance to autism.

Professor David Skuse  
*Institute of Child Health*

Funding from a number of organisations on autism research (not the MRC). 
Colleagues have interest in immunisation policy, including MMR and autism.

Ms. Catherine Burkin  
*Lay Observer*

Ms. Donna Williams  
*Lay Observer*
Lay Group

Ms. Judith Barnard
Employed by National Autistic Society.

Ms. Virginia Bovell
Trustee of PACE.
Trustee of the TreeHouse Trust.
Parent of an autistic child.

Ms. Catherine Burkin
Employee of National Autistic Society.
Grant holder with Department of Work and Pensions.
Collaboration with P Howlin on evaluative research study (not MRC).

Mr. Adam Feinstein
None

Ms. Elaine Kay
None

Ms. Rosemary Kessick
Litigant in class action against MMR manufacturers.

Mr. Donald Liddell
None

Ms. Helen Millar
None

Mr. David Potter
Employee of The National Autistic Society: responsibility for autismconnect.org
Links with Autism Research Centre (Cambridge); Autism Research Unit (Sunderland); PACE; Institute of Child Health.

Mr. Jonathan Sussex
Employee of Office of Health Economics (part Association of British Pharmaceutical Industries).

Ms. Su Thomas
Parent of an autistic child.

Mr. Jonathan Tommey
Parent of an autistic child.

Ms. Donna Williams
None

* # alternatives
External Expert Advisors

Professor John Cummings
Tayside University Hospitals
NHS Trust

Reverend Graham Forbes
Provost of St. Mary's Cathedral

Professor Christopher Gillberg
University of Gothenberg

Ms. Jill Murie
Public Health,
Institute of Scotland

Professor Sir Michael Rutter
Institute of Psychiatry

Ms. Jill Murie
Public Health,
Institute of Scotland

Professor Emily Simonoff
GKT Medical School

Professor Walter Spitzer
McGill University, Canada

None.
St. Mary's has Glaxo-Wellcome shares in it's portfolio.
Chair of Scottish Executive Expert Group on Immunisation.

Co-ordinator of Scottish National Needs Assessment on Autistic Spectrum Disorders.

Member of International Molecular Genetic Study of Autism Consortium.
Advisor to defendant in legal case.
Deputy Chairman and Governor of Wellcome Trust.
Funding from Helmut Horten Foundation and Department of Health.
Member of National Autistic Society and vice-president of Association for All Speech Impaired Children.

Funding from organisations for autism research (not MRC).

Advisor to claimants involved in legal action.
Glaxo and Merck Shareholder
Scientific Advisor to Sponsor of the Intercontinental Case Control Study on Autism and Vaccines.
APPENDIX 1 ANNEX 4

MRC REVIEW GROUP ON AUTISM RESEARCH:
EPIDEMIOLOGY AND CAUSES

Terms of Reference

Purpose and Outcome

The aim of the Review is to provide the Department of Health (in the first instance) with a clear picture of current state of knowledge about the epidemiology and causes of ASDs, and an understanding of the strength of the evidence underpinning that knowledge. It aims to help the government to answer questions such as, If MMR vaccination is not a cause of ASDs, then what is? Is ASDs increasing in the population? and What research needs to be stimulated?

Both the process of the Review and the final Report will aim to ensure accessibility and acceptability of the findings to the lay public, as well as accurately reflecting expert opinion. This does not mean that we will achieve a single consensus view.

Scope of the Review

1. To review current knowledge (both nationally and internationally) on the following themes:
   • EPIDEMIOLOGY: the incidence and prevalence of autistic spectrum disorders
   • The possible CAUSES of autistic spectrum disorders, including mediating factors that may influence the nature and extent of impairment and social disadvantage, and
   • The evidence-base for INTERVENTIONS (focusing on those that are informed by, or that inform, understanding of causes).
2. To identify gaps in the biomedical, psychological and behavioural knowledge base.
3. To suggest possible research areas for further development.
4. To encompass expert and lay understanding and experience of ASDs in appraising the evidence base.
5. Social care, education and organisation and delivery of services will generally be outside the scope of the review.

Notes on working method

1. Three Expert Subgroups will be established to cover the areas of:
   • Epidemiology and case definition
   • Physiology and infections
   • Psychology and behaviour
2. The Subgroups will report to the overall Chairman of the Review through the Subgroup chairmen. Information will be shared across the Subgroups, the steering group and to MRC officers, as well as to the MRC Consumer Liaison Group. The work of the group will otherwise be confidential.
3. The Lay Group will have observers on the Expert Subgroups. The Lay members roles are to
   • advise on effective ways for lay and parental participation in the review;
   • contribute to the work of the Expert Subgroups, particularly through identifying coherent sets of questions to be put to the researchers;
   • advise on effective reporting and dissemination of the review so that it can address the needs of both the Department of Health and the wider lay audiences.
4. MRC Head Office will support the work of the group in particular its meetings, which will be minuted in brief (along the lines of: key points, submissions, declarations of interest, decisions and action agreed). A verbatim record will not be kept.
5. The Office will also establish an e-mail list for communications and a list of information resources.
6. MRC Head Office is responsible for communicating the work and findings of the review groups to the Department of Health and externally.
## APPENDIX 2
Submitted and Suggested Information

The following table lists information that was suggested by members of the public, Lay or Expert Groups, which they considered might be helpful to the Review.

### List of Published and Unpublished Works

<table>
<thead>
<tr>
<th>Name</th>
<th>Name of Published or Unpublished work</th>
</tr>
</thead>
</table>
                           | › Final Report - Sensori Motor Training Project - National Association of Retarded Children together with reference documents  
                           | › Burn, J. Carina’s Story.  
                           | › Email from David Delacato  
                           | › Awaiting English Translation of Parisi, A. I bambino dallo sguardo sfuggente. |
| Challoner, A.            | › Autism Review Report - A collection of papers and other relevant information.* |
Dealler, S.  
- Dealler, S., Carrington, S., Baird, A., Reid, C. & Corfield, A.  
  *Autism: the significance of sulphate metabolism and sulphotransferase activity in the pathogenesis of the syndrome and potential therapeutic measures that this may permit.*  
- Dealler, S. Research into ASD. The time has come for major research into the background biology of the disorder.

Desorgher Mrs S.  
- Desorgher Mr and Mrs. Autism, Pulling it all together.  
- Desorgher Mr and Mrs. Autism, Pigments and the Immune System.  
  Desorgher website: http://www.desorgher.fsnet.co.uk

Fombonne Dr. E.  
- Chen W. et al. No evidence for links between Autism and measles virus. 2001 (submitted)  
› Fombonne, E. Epidemiological surveys of Autism: a review. 
_Psychological Medicine_ 1999; 29: 769-786

› Fombonne, E. What is the prevalence of Asperger disorder? 
_Journal of Autism and Developmental Disorders_ June 2001

› Wing L. The definition and prevalence of Autism: a review. 
_European Child and adolescent Psychiatry_ 1993; 2: 61-74


Fraser, Prof. W.


Johnstone, Prof. E.

› Letter from Rear Admiral John Adams to Secretary of State, Alan Milburn.

McCarthy, G. I. M.


Monaco, Prof. A.

› The International Molecular Genetic Study of Autism Consortium. A full genome screen for Autism with evidence for linkage to a region on chromosome 7q. _Human Molecular Genetics_ 1998; 7:571-578


› The International Molecular Genetic Study of Autism Consortium. Further characterisation of the Autism susceptibility locus AUTS1 on chromosome 7q. _Human Molecular Genetics_ 2001; 10:973-982

› The International Molecular Genetic Study of Autism Consortium. A genome wide screen for Autism; Strong evidence for linkage to chromosomes 2q, 7q and 16p. _Am J Human Genetics_ 2001; (in revision).
Murch, Dr. S.


Murray Ms D.

- Lesser M. and Murray D. The Interest System, a new conceptual nervous system: implications for Autism. Short version presented 23rd June 2001 at the Nexus Workshop with the Central European University Budapest, “Living With Limits to Knowledge”.
- Longer version prepared for submission to Autism Int. will be available by July 11th.

Scott, Dr. F.


Shattock, Mr. P.

- Shattock, P. Evidence submitted to the MRC “Causes of Autism” Committee (Physiology).

Skuse Prof. D.

Stokes, Prof. C.  

Tommey, Mr J.  

Waring, Dr. R.  

Williams Ms D.  
› Kenyon. Dr J. Research into neurotransmitter imbalance, links with neurotoxins, leaky gut, immune deficiency etc. see [www.doveclinic.com](http://www.doveclinic.com)

* Submitted to Expert Groups as hard copy
## APPENDIX 3

### List of Individuals Specifically Approached by Review

<table>
<thead>
<tr>
<th>Individual</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dr A Wakefield</strong></td>
<td>Did not wish to submit</td>
</tr>
<tr>
<td>Centre for Gastroenterology</td>
<td></td>
</tr>
<tr>
<td>Royal Free Hospital School of Medicine</td>
<td></td>
</tr>
<tr>
<td><strong>Professor S Gupta</strong></td>
<td>E-mail received 8/8/2001*#</td>
</tr>
<tr>
<td>Division of Basic &amp; Clinical Immunology</td>
<td></td>
</tr>
<tr>
<td>University of California, Irvine</td>
<td></td>
</tr>
<tr>
<td>Developmental Pediatrics</td>
<td></td>
</tr>
<tr>
<td>Children’s Hospital Richmond, Virginia</td>
<td></td>
</tr>
<tr>
<td><strong>Professor J O’Leary</strong></td>
<td>No response as of 20 / 9 / 2001</td>
</tr>
<tr>
<td>Coombe Women’s Hospital, Dublin</td>
<td></td>
</tr>
<tr>
<td><strong>Dr R Sandler</strong></td>
<td>No response as of 20 / 9 / 2001</td>
</tr>
<tr>
<td>Rush Children’s Hospital</td>
<td></td>
</tr>
<tr>
<td>Rush Medical College, Chicago</td>
<td></td>
</tr>
<tr>
<td><strong>Mr P Shattock</strong></td>
<td>Submitted information*#</td>
</tr>
<tr>
<td>Autism Research Unit</td>
<td></td>
</tr>
<tr>
<td>University of Sunderland</td>
<td></td>
</tr>
<tr>
<td><strong>Dr R Waring</strong></td>
<td>Submitted information*</td>
</tr>
<tr>
<td>Department of Biochemistry</td>
<td></td>
</tr>
<tr>
<td>University of Birmingham</td>
<td></td>
</tr>
</tbody>
</table>

* Submitted to Expert Groups as hard copy

# Information submitted was treated in confidence
MRC Autism Review: 11 July Workshop

**AIM:** A preliminary exploration of the main scientific issues and of the questions presented by the Lay Group, for consideration by the Review.

09.00  **Registration**

09.30  **Introductory Session** (Eve Johnstone)

09.50  **Current Research Issues for Autism**
This session aims to explore the broad issues for research.

09.50  Introduction to the Session

10.00  **Panel: Case Definition & Epidemiology** (Chair Carol Dezateux)
Perspectives from Lorna Wing and Eric Fombonne
Followed by 30 minute open discussion

11.20  **Panel: Physiology & Infections** (Chair Derek Jewell)
Perspectives from Bert Rima, Ian Sanderson, Simon Murch
Followed by 30 minute open discussion

12.40  **Lunch**

13.40  **Panel: Genetics, Brain and Behaviour** (Chair Uta Frith)
Perspectives from Patrick Bolton (genetics), Tony Bailey (brain)
and Tony Charman (psychology & behaviour)
Followed by 30 minute open discussion

15.00  **Tea**

15.20  **Lay Group Perspectives** (Judith Barnard, Elaine Kay, and Donna Williams)
Presentation & discussion of the issues and questions identified by the Lay Group.

15.50  **Communication and Dissemination Strategy** (Elizabeth Mitchell)
Communication to the Department of Health and to wider scientific and lay communities.

16.05  **Panel Discussion:**
**Taking the Review Forward** (Eve Johnstone)

16.20  **End**
MRC Autism Review: 26 September Synthesis Meeting

LOCATION: The Novartis Foundation, 41 Portland Place, London W1B 1BN

AIM: A discussion of the draft submissions from members of the Expert Groups, for the purpose of bringing together the various themes of the Review, in consideration of the questions presented by the Lay Group.

Agenda

09:30  Registration / Tea & Coffee

10:00  Individual Expert Group Meetings
       Case Definition & Epidemiology
       Physiology & Infections
       Brain and Behaviour

12:15  Preliminary Joint Session

12:30  Lunch

       Joint Session of Expert Groups

       Presentations from the Subgroups, followed by open discussion

15:30  Tea

15:50  Identification of further action

16:30  END
MRC Autism Review: 5 November Strategy Meeting

LOCATION: The Novartis Foundation, 41 Portland Place, London W1B 1BN, from 10.00 to 17.00.

Programme

1) Chairman’s Welcome


3) Presentations from Expert Group Chairs: Brief overviews from Carol Dezateux, Derek Jewell, Uta Frith and Lay Group – highlighting (1) preliminary conclusions and recommendations from their groups, (2) key issues in relation to the Lay Group Questions, and (3) key issues for the research strategy discussion.

4) Short Plenary Discussion – to identify cross-cutting issues and any gaps for further discussion later in the day.

5) International & National Strategies & Reviews - External perspectives

   Brief presentations from:
   • USA perspective – Peter Dukes
   • Christopher Gillberg: A Scandinavian perspective
   • Jill Murie (Scotland): Review of Autism Services Scotland
   • Graham Forbes (Scottish Executive Review)
   • Anne Le Couteur: (National Initiative for Autism Screening and Assessment)

6) Invited Commentaries on the Draft Strategy

   • Walter Spitzer (Emeritus Professor, McGill University)
   • John Cummings (Tayside University Hospital NHS Trust)
   • Michael Rutter (Institute of Psychiatry) (Retired) (written) – introduced by Professor Johnstone
   Followed by short discussion

7) Preliminary Identification of Strategic Issues (From 12.45): Identification of the main strategic issues for autism research for detailed consideration in the afternoon session.

LUNCH
8) **Research Strategies:** Assisted by the external visitors, the Review Members tasked with developing a broad, forward-looking strategy for autism research in the UK. It will be helpful to approach this through identification of

- **Strategic research questions** building on the Review’s earlier work integrating perspectives of researcher and users
- Appropriate (and inappropriate) methodologies to address those questions
- How best to achieving the interdisciplinarity required to deliver the strategic research objectives
- How best to develop the other interfaces critical to an integrated strategy: parent / researcher / practitioner knowledge and expertise; the health and education domains; “grey” / white evidence.
- Strengths and gaps in UK research capacity and infrastructure – including in the clinical/service structures that will essential to advancing the research strategy.
- **Ethical issues**
- **Sequencing** and co-ordination issues within the strategy – early priorities, developmental work required…

9) **Conclusions and Recommendations:** The Review Group will need to identify the main conclusions & recommendations that fall out of the previous discussions.

10) **Identification of Further Actions:** (1) For completion of the Report by end of November; (2) For disseminating the Report; (3) For facilitating activities recommended or arising from the Report.

11) **Closing Remarks**

- Virginia Bovell / Judith Barnard
- Eve Johnstone
Research Methodology Workshop July 9 2001

TRAINER: Sally Crowe, Public Health Research Unit Oxford
ATTENDING: members of MRC Autism Review Lay Group

Learning Objectives:

1) To be able to describe a variety of research methodologies and understand the importance of framing and building the research question
2) To develop and practice critical appraisal skills
3) To have discussed systematic reviews, including aspects of bias and the use of unpublished literature
4) To have considered uncertainties in research and how this affects decision making
5) To enable participants to feel more confident and competent in their discussions with the expert review groups
6) To have networked and had some fun

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.45</td>
<td>Introductions and expectations of the day</td>
<td>Jargon buster handout</td>
</tr>
<tr>
<td>10.00</td>
<td>Framing and building a research question using an Autism example</td>
<td>Slide handout</td>
</tr>
<tr>
<td></td>
<td>A birds eye view of research methods</td>
<td></td>
</tr>
<tr>
<td>10.00</td>
<td>Systematic Reviews what are they?</td>
<td>Slide handout</td>
</tr>
<tr>
<td>11.30</td>
<td>Tea/Coffee break</td>
<td></td>
</tr>
<tr>
<td>11.45</td>
<td>Working with uncertainty in research - examples and discussion</td>
<td></td>
</tr>
<tr>
<td>12.30</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>1.15</td>
<td>Critical appraisal skills, what are they how can they help? 10 questions</td>
<td></td>
</tr>
<tr>
<td>1.45</td>
<td>Small group work appraising a relevant article (need to discuss)</td>
<td>Research/info article</td>
</tr>
<tr>
<td>2.45</td>
<td>Tea/Coffee break</td>
<td></td>
</tr>
<tr>
<td>3.00</td>
<td>Feedback from small groups, the key components of appraising information</td>
<td></td>
</tr>
<tr>
<td>3.45</td>
<td>Summing up of the day, evaluation</td>
<td></td>
</tr>
<tr>
<td>4.00</td>
<td>Depart</td>
<td></td>
</tr>
</tbody>
</table>

- The style of the day will be interactive with focused activity as well as more ‘freeflow’ sessions.
- There will be handouts for all the key learning points; a suitable folder will be supplied to keep them in.
APPENDIX 5

Lay Group Questions

Epidemiology

• What is the definition of ASDs spectrum used by this Review? See Chapter 3.

• How many people have an ASDs spectrum condition? See Chapter 4.

• Can changes in diagnostic practice alone explain the perceived increase in numbers of people with an ASDs spectrum condition? See Chapter 4.

• Would a national register prove a more reliable and consistent way of keeping track of changes in prevalence? See Chapter 4.

• Is the male-female ratio in ASDs spectrum conditions consistent across sub groups? See Chapter 4.

• Is there any evidence for differences in the distribution of the condition over different socioeconomic groups or demographic areas? See Chapter 4.

• What information is there as to the increase in diagnoses of ASDs in countries using the triple MMR vaccine and those immunising separately with single, monovalent vaccines? The Review did not consider this specific question.

Case definition

• How much does a child’s diagnosis depend on the route through the health care system s/he follows? The Review did not directly consider this question, which is related to issues of service delivery. However, as discussed in the Report, a diagnosis of an ASD can be made accurately using existing assessment tools.

• Given that assessments are psychologically based is genuine assessment of children with ASDs possible? How reliable are the tests and measures performed on children with ASDs? At present there is no biological marker or test for ASDs, and it is unlikely that a single genetic “test” would correctly identify an individual with an ASD, for the reasons given in the Report. The current psychological diagnostic tools have been rigorously tested and independently validated. There are numerous biochemical tests and analyses which have been proposed to be diagnostic for ASDs, but these remain to be independently validated.

• Families with an autistic child are given an approximate 6% chance of having another born with the disorder. Is this a true figure and what is its significance? See Chapter 5.

• Can an understanding of the genetics and aetiology of serious allergies help with understanding ASDs spectrum conditions? The Review was not able to consider this question. However, the immunological status of individuals with ASDs is currently an area of uncertainty.

• Late onset ASDs – is it real or a consequence of poor initial diagnosis? See Chapter 3.

• Reliability of diagnosis – high functioning autism vs. autism See Chapter 3.
• What is the evidence that MMR does not cause ASDs? Is there a way of getting an upper limit on a subgroup of autistics who might have been caused by MMR? See Chapter 5.

• Is the gender difference due to diagnostic bias? See Chapter 4.

• How early can you identify an autistic child? See Chapter 3.

• Why does it take 2 years to get a diagnosis? There are a number of factors to be taken into account when considering the time taken to get a diagnosis. Parents may not always seek help immediately. Once professional bodies are apprised of potential problems, a diagnosis of ASDs/ASD requires a multi-disciplinary assessment undertaken across multiple settings. This takes time by necessity. Furthermore, parents need time to work through the implications of the diagnosis and the practical consequences.

• Can regressive ASDs be considered a specific subtype of ASDs? See Chapter 3.

• What proportion of total cases are regressive? See Chapter 3.

• What is the relationship between ASDs and the extended Landau Kleffner syndrome? See Chapter 5.

Physiology and infections

• What role has disordered bowel function played in ASDs? What is the evidence that gastrointestinal disorders, eg ‘leaky gut’, are associated with ASDs spectrum disorders? What research is needed to strengthen our understanding of any relationship between gastrointestinal disorders and ASDs, and between ASDs and gastrointestinal disease? See Chapter 5.

• Are there environmental triggers to ASDs? Are there diets that trigger, prolong or ameliorate ASDs? See Chapter 5.

• What evidence is there implicating vaccines in ASDs? See Chapter 5.

• What is known from drug based interventions about the causes and the underlying physiological processes in ASDs? See Chapter 5.

• What does knowledge of animal models tell us about the condition of ASDs in people? See Chapter 5.

• What is the evidence for Borna disease as a causative agent? See Chapter 5.

• In what ways does the physiology of people with ASDs differ from other people? See Chapter 5.

• What does research tell us about ASDs in relation to the following: Immunology (allergies and vaccines); Biochemistry (endocrine disruption, toxicology); Infections (viral) and complex disorders (eg. Myalgic encephalopathy, chronic fatigue syndrome); Stress; Inflammatory conditions (eg Rheumatoid arthritis); Nutrition and diet (effective nutrients or diet, state of the gut). How biologically plausible are such associations? See Chapter 5.

• What is the impact of a predominance of repeated antibiotic use for respiratory tract infections and glue ear? The Review did not have access to specific published reports on this issue, and have not therefore been able to comment on this question.
From our understanding of the causes and epidemiology of ASDs what biochemical or physiological tests might be valuable? Could mercury (especially in the form of thiomersal) be implicated as a trigger of ASDs? See Chapter 5.

Why do 20% of autistic children suffer epileptic fits in adolescence? Would there be a rationale for prescribing anti-epileptics pre-emptively? See Chapter 5.

What role do obstetric complications (e.g. forceps, prolonged labour) have in autism? See Chapter 5.

Psychology and behaviour

In what ways do the brains of people with ASDs differ from other people? See Chapter 5.

How can knowledge of the brains of people with ASDs be applied to interventions to improve the quality of life? Knowledge of what cannot be learned easily (because the necessary neural mechanism is not functioning well) can lead to the rational provision of compensatory learning opportunities. Compensation includes the possibility that others act as appropriate support for individuals with ASDs. Improved understanding of the brain abnormality (even if it is at present incurable) should lead to greater public awareness of the gravity of the disorder.

What do theories of differences in executive function and central coherence have to tell us about the condition? What knowledge and theories link what is known about genetics and physiology to psychological theories, such as theory of mind? What do we know about information processing problems in ASDs? See Chapter 5.

What evidence is there that psychological therapies address the underlying pathophysiology of ASDs? The Review were not able to consider this question.

Is autism one end of the normal spectrum of behaviour, or is it an abnormal condition? See Chapter 3

What is the evidence for the success of early interventions? See Chapter 5.

What can we learnt from other brain conditions / injuries (e.g. Alzheimer’s)? Accidental damage to specific brain regions can result in problems with theory of mind. Brain abnormality underlying schizophrenia can also mimic certain symptoms (negative symptoms) and can result in problems with theory of mind. Analogies between developmental and acquired disorders need to be drawn with care.

What evidence exists on autistic individuals having an alternative form of perceptual processing (e.g. auditory processing)? See Chapter 5.

What data exists on dual diagnosis (e.g. ADHD) with ASDs? See Chapter 5

What are the differences in autistic brains, compared to others? What areas of the brain are affected, and are they always the same regions? Is retardation caused by damage to different areas? See Chapter 5.