INFANTILE AUTISM: A GENETIC STUDY OF 21 TWIN PAIRS

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INTRODUCTION

In his original description of the syndrome of infantile autism, Kanner (1943) noted that the condition was distinctive in that, in most cases, the children's behaviour had appeared abnormal right from early infancy. He suggested the presence of an inborn defect of presumably constitutional origin. Since then, there have been numerous hypotheses concerning the possible nature and origins of this defect (see Ornitz, 1973; Rutter, 1974). However, in spite of the supposition that the disorder is inborn, there have been surprisingly few attempts to investigate possible genetic influences.

The first set of evidence comes from family studies. There is no recorded case of an autistic child having an overtly autistic parent and it is decidedly unusual for a family to contain more than one autistic child, although such cases have been reported (Seidal and Graf, 1966; Verhees, 1976). The usually negative family history for autism seems to be out of keeping with genetic determination. However, this line of reasoning is fallacious. First, it is extremely rare for autistic persons to marry (Rutter, 1970) and there is only a single published report of one having given birth to a child (Kanner and Eisenberg, 1955). This fact alone invalidates the usual assumptions about the meaning of a family history. Second, autism is a very uncommon disorder, occurring in only about 2-4 children out of every 10,000 (Brask, 1967; Lotter, 1966; Wing et al., 1976). If the population frequency is very low, the rate in relatives will also be low even in conditions with a high heritability (Smith, 1974; Curnow and Smith, 1975). On both these grounds a strong family history would not be expected even if autism was largely genetically determined.

Moreover, there are two positive findings from family history studies which do suggest possible hereditary influences. First, although the best available estimate indicates that only about 2 per cent of the siblings of autistic children suffer from the same condition (Rutter, 1967), this rate is 50 times that in the general population. Second, although a family history of autism is very rare, a family history of speech delay is much more common, being present in about a quarter of cases (Bartak et al., 1975; Rutter et al., 1971). This last observation raises the possibility that it is not autism as such which is inherited but rather that the genetic influence concerns some broader linguistic or cognitive impairment of which autism is but one part.

The second set of evidence comes from twin studies. These were reviewed 10 years ago (Rutter, 1967), with the conclusion that no valid inferences could be drawn. Since then, there have been several further reports (McQuaid, 1975; Kotsopoulos, 1976; Kean, 1975), but the conclusion remains the same (Hanson and

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297
Gottesman, 1976). The problems in interpretation are two-fold. First, the reports of monozygotic pairs far outnumber those of dizygotic pairs (22 compared with 10). As dizygotic pairs are twice as frequent in the general population, it is clear that there must have been serious selective biases in reporting.* This is sufficient in itself to disregard the findings. Second, excluding two pairs where the autism is associated with an overt physical disorder (Kallman et al., 1940; Keeler, 1958) only five papers reporting same sexed pairs include both an adequate clinical description and evidence of zygosity (Bakwin, 1954; Kamp, 1964; McQuaid, 1975; Ward and Hoddinott, 1962; Vaillant, 1963). For what it is worth, these show two out of three concordance for monozygotic and one out of two concordance for dizygotic twin pairs. In addition, there are two opposite sexed pairs, one concordant (Kotsopoulos, 1976) and one discordant (Böök et al., 1963). The great majority of the remainder report concordance in monozygotic pairs, but the papers lack either clinical details or evidence of zygosity and many are no more than passing references in publications on other topics (Chapman, 1957, 1960; Creak and Ini, 1960; Ornitz et al., 1965; Polan and Spencer, 1959; Sherwin, 1953; Bruch, 1959; Keeler, 1957, 1960; Lovas et al., 1965; Lehman et al., 1957; Brown, 1963; Weber, 1966; Stutte, 1960). The same problems apply to reports of twins with childhood schizophrenia (Havelkova, 1967; Cline, 1972). O’Gorman (1970) has described two monozygotic pairs concordant for “pseudo-schizophrenia” but the criteria for zygosity were not specified.

In studying genetic factors, it is necessary to bear in mind that autism is probably a behavioural syndrome with multiple aetiologies (Rutter, 1974). Certainly, it is known that the syndrome can develop in association with medical conditions as pathologically diverse as congenital rubella (Chess et al., 1971) and infantile spasms (Taft and Cohen, 1971). Accordingly, the investigation of possible hereditary factors must take account of aetiological heterogeneity.

The need was apparent for a systematic and detailed study of a representative sample of twin pairs containing an autistic child. Because of the possibility that the genetic factor might apply to a broader range of disorders than autism per se, it would be essential to obtain detailed assessments of social, emotional, cognitive and linguistic functions in the non-autistic as well as the autistic twins. This demanded a personal study of the twins. Because twins are especially liable to suffer perinatal complications and because such complications have been thought to play a part in the aetiology of autism, it would also be necessary to obtain obstetric and neonatal data in order to check whether the concordance findings were a consequence of physical environmental factors rather than heredity. This is what we set out to do, and the present paper reports the findings.

**METHODS**

(a) Subject selection

The first task was to obtain a complete and unbiased sample of same-sexed twin pairs which included an autistic child. Opposite-sexed pairs were excluded in view of the well-established finding that autism is very much commoner in boys. A list of autistic twin pairs collected over the years by the late Dr. M. Carter provided the start. Then we sought, using multiple sources of information, to obtain information on all school age autistic twin pairs in Great Britain. Letters and personal

*Unless MZ twins were peculiarly liable to autism, which seems implausible.
approaches were made to psychiatric and paediatric colleagues known to have a special interest in autism or who were consultants to special schools which catered for autistic children. A request for cases was also made to all members of the British Child Psychiatry Research Club. Through the Association of Head Teachers of Schools/Classes for autistic children, approaches were made to those running special schools or units for autistic children in Britain. Mrs. Monica White kindly searched the records of all children known to the National Society for Autistic Children, to identify all who were twins. A request for cases was also published in the Society Newsletter. Finally, a personal search was made, using the twin registers at the Maudsley Hospital and at the Hospital for Sick Children, London.

In this way, 33 possible pairs were identified and a detailed scrutiny was made of all available case notes and other clinical information. The sample was restricted to cases which might meet the clinical diagnostic criteria for autism outlined by Kanner (1943) and further delineated by Rutter (1971, 1977), namely, a serious impairment in the development of social relationships of the type characteristic of autism (that is with limited eye to eye gaze, poor social responsiveness, impaired selective bonding, a relative failure to go to parents for comfort, and, when older, a lack of empathy, a lack of personal friendships and little group interaction); together with delayed and deviant language development with some of the specific features associated with autism (namely poor language comprehension, little use of gesture, echolalia, pronominal reversal, limited social usage of language, repetitive utterances, flat or staccato speech and very restricted imaginative play); and also stereotyped, repetitive or ritualistic play and interests (as indicated by an abnormal attachment to objects, marked resistance to change, rituals, repetitive behaviour, unusual preoccupations and restricted interest patterns). Cases with an onset after age 5 years were excluded, but no further restriction was placed in terms of age of onset. Because this was a genetic study, children whose autism was associated with a known diagnosable neurological disorder (such as tuberous sclerosis or cerebral palsy) were also ruled out.

<table>
<thead>
<tr>
<th>Sole source</th>
<th>Joint source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Carter's list</td>
<td>7</td>
</tr>
<tr>
<td>National Society</td>
<td>9</td>
</tr>
<tr>
<td>Schools</td>
<td>4</td>
</tr>
<tr>
<td>Maudsley Hospital Register</td>
<td>3</td>
</tr>
<tr>
<td>Hospital for Sick Children Register</td>
<td>3</td>
</tr>
<tr>
<td>Individual psychiatrists</td>
<td>12</td>
</tr>
<tr>
<td>Newsletter advert</td>
<td>0</td>
</tr>
</tbody>
</table>

On the basis of information in case notes, eight twin pairs were excluded leaving a sample of 25 twin pairs to be studied in detail. After the children and parents had been seen and interviewed by one of us (SF), diagnoses were then made using all available data. At that final stage, a further four pairs were excluded, leaving a sample of 21 same-sexed pairs ranging in age from 5 to 23 years (six aged 5-9 years, eight aged 10-14 years and seven aged 15+ years). Table 1 gives the sources of selection for these 21 pairs, which constitute the basis of this paper. In a third of cases, the names were available from just one source, but most cases were notified by several different sources. It is clear that no one source would have been adequate.

(b) Zygosity

Zygosity was determined by physical appearance, fingerprints and blood grouping. Attention was paid to such detailed physical characteristics as eye colour and pattern of iris; hair colour, texture and curliness; and shape of nose, ears and hands as well as general appearance (Gedda, 1961). In eight of the pairs, the differences between the twins were sufficiently marked to be sure of dizygosity without the need for further testing. In two pairs, a designation of monozygosity was made on the basis of very close physical similarity plus the results of fingerprint analysis using the ridge count method described by Holt (1961). Blood groups testing (Race and Sanger, 1975) was undertaken for 12 pairs,* nine of which proved to be monozygotic. Thus, the sample consists of 11 monozygotic and 10 dizygotic pairs.

*In two pairs, the blood tests showed that the parents' view of zygosity was wrong.
(c) **Data collection**

In all cases, an attempt was made to interview the parents, using a standardized interview and also to interview and examine both twins. Complete information was obtained in 19 pairs. In one case, the parents and the autistic twin were interviewed but the normal twin was not seen, in a second no interview was undertaken. However, in both cases where personal interviewing was incomplete, the children had been previously studied very extensively and detailed descriptions, findings and photographs were made available to us.

Topics covered in detail by the parental interview included a systematic account of the children's social, emotional and behavioural development and present status; language development, competence and characteristics; early history and developmental milestones; account of pregnancy, labour and perinatal period; illnesses and separations; family characteristics and social circumstances; and family history of psychiatric and neurological disorder. Vineland Social Maturity Scale (Doll, 1947) and Mecham Language Scale (Mecham, 1958) assessments were also undertaken.

The children were closely observed and interviewed at home or in hospital and all were given a detailed neuro-developmental examination. If systematic psychological test findings were not readily available, further testing of cognition and language was undertaken using the Wechsler (1949), Merrill-Palmer (Stutsman, 1948) and Reynell (1969) scales.

Paediatric and psychiatric case records were obtained and studied for all hospital admissions and attendance. Finally, hospital obstetric records were examined for all but one of the 17 twin pairs born in hospital.

(d) **Diagnosis of autism**

Systematic biases readily arise in twin research through the possibility of the psychiatric diagnosis of one twin being influenced by knowledge on his co-twin and on the zygosity of the pair. Accordingly, rigorous precautions were taken in the study to ensure that such diagnostic contamination could not occur. The procedure was as follows. First, one of us (S.F.) prepared a detailed separate summary of all available psychiatric and developmental information for each of the twin children included in the study. These summaries were then carefully scrutinized to ensure that all possible identifying information (such as family characteristics) were deleted. As a further precaution, the age of the child was given only in terms of a 5-year grouping. The case histories were then put into random order and given a new case number so that it was no longer possible to sort by pairs. These randomized case histories without identifying information were then given to the other investigator (M.R.) for diagnosis, made “blind” both to pair and to zygosity. His diagnoses are those used for the purposes of all analyses.

Autism was diagnosed on the basis of the strict criteria already outlined. As noted, at this stage, the sample was reduced to 21 pairs including 25 autistic children as a result of these “blind” diagnoses. Fourteen children were diagnosed as showing typical and characteristic infantile autism.* A further 11 met the criteria for autism, but the clinical picture was somewhat atypical in some way. Thus, in one child the onset was not until the age of 3½ years; in another child the course was unusual in that almost all autistic features were lost by the age of 6 years (interestingly, he was otherwise fairly typical except that an air encephalogram showed cortical atrophy); and other children were atypical in terms of more social responsiveness or less ritualistic activity than usual.

A separate diagnosis of cognitive/linguistic impairment was made on the basis of at least one of the following features: lack of phrase speech by 30 months, a verbal I.Q. or social quotient of 70 or below, grossly abnormal articulation persisting to age 5 years or older and scholastic differences of such severity as to require special schooling. All 25 autistic children met at least two of these criteria and a further six non-autistic children also did so.

Finally, a psychiatric assessment was made with respect to any non-autistic disorders which were present. In view of its possible connection with infantile autism, particular attention was paid to the possible presence of so-called “autistic psychopathy” meaning a condition characterized by gross social impairment, obsessive preoccupations or circumscribed interest patterns and poor coordination but normal general intelligence (van Krevelen and Kuipers, 1962; van Krevelen, 1963).

*The original “blind” diagnoses gave only 12 cases, but further information made available later on one concordant pair caused them to be transferred from the atypical to the typical category. This change does not affect the concordance findings.
DESCRIPTION OF SAMPLE

(a) Typical–atypical differentiation

In view of the uncertainty whether the typical–atypical differentiation had any validity or meaning, the clinical features of these two subgroups were systematically compared (see Table 2). Very few differences were found apart from the items which led to the group being classified as atypical. Thus, there were no marked differences in terms of sex, I.Q., language abnormalities or social class, and there were only marginally fewer repetitive and stereotyped symptoms. The main difference was that the atypical children showed less severe social abnormalities and four of them had an onset after 30 months (by definition none of the typical children had such a late onset). Also, biological hazards were slightly (but not significantly) less common in the atypical group. In view of the fact that, in most respects, the typical and atypical children were so similar, these two subgroupings are combined in presenting the results.

(b) Comparison with non-twin samples

The 21 twin pairs gave rise to 25 cases of autism. As is evident from Table 2 and from the case histories in the Appendix, the behavioural characteristics of the autistic twins were closely comparable to non-twin samples. Table 3 shows how other features compare with a study of singletons previously undertaken by one of us (Rutter et al., 1967).

Of the 25 autistic children, 19 were male, giving a male : female ratio of 3:1 to 1 which is similar to most other studies. The parents came from all social strata but were predominantly middle class, which is in line with most other series. Other family characteristics were also much as expected. Thus none of the parents suffered from schizophrenia and only one (case 19) of the 36 sibs was autistic (a rate of 2.8%). However, in three of the 21 families (14%) either a parent or sib had experienced a severe delay in the acquisition of spoken language (cases 2, 10 and 14).
TABLE 3. SEX, I.Q., AND SOCIAL CLASS

<table>
<thead>
<tr>
<th>Sex ratio</th>
<th>Twins (this study)</th>
<th>Singletons (Rutter et al., 1967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.Q.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>48-0%</td>
<td>43-0%</td>
</tr>
<tr>
<td>50-69</td>
<td>20-0%</td>
<td>28-5%</td>
</tr>
<tr>
<td>70+</td>
<td>32-0%</td>
<td>28-5%</td>
</tr>
</tbody>
</table>

Social class

<table>
<thead>
<tr>
<th>Twins (this study)</th>
<th>Singletons (Rutter et al., 1967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II</td>
<td>57-0%</td>
</tr>
<tr>
<td>III</td>
<td>28-5%</td>
</tr>
<tr>
<td>IV and V</td>
<td>14-5%</td>
</tr>
</tbody>
</table>

About half the autistic children were severely retarded, but nearly a third had an I.Q. in the normal range on non-verbal tests, which again is closely comparable to other findings. By definition, none of the children had a diagnosable neurological condition. However, two-thirds showed impairment on developmental functions such as motor coordination or had isolated minor signs such as strabismus or choreiform movements. Four of the autistic children had developed epileptic fits during adolescence. In 11 cases, EEGs had been reported as abnormal, but, in most cases, the abnormalities were of a non-specific nature. Air encephalograms had been undertaken in three children; these showed left-sided cortical atrophy in one case, slight dilatation of the right lateral ventricle in a second case and no abnormality in a third. It may be concluded that, apart from the fact that they are twins, the 25 autistic children in the sample are closely similar to the autistic children described in non-twin populations.

RESULTS

(a) Concordance for autism

Of the 10 dizygotic twin pairs, none was concordant for autism, whereas four of the 11 monozygotic pairs were concordant (Exact test; \( P = 0.055 \)). This gives

<table>
<thead>
<tr>
<th>MZ pairs (n = 11)</th>
<th>DZ pairs (n = 10)</th>
<th>MZ–DZ difference (Exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance for autism (%)</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Concordance for cognitive disorder (including autism) (%)</td>
<td>82</td>
<td>10</td>
</tr>
</tbody>
</table>

a 36% concordance rate by pair or a 53% concordance rate by proband for MZ pairs and in each case a zero per cent concordance for dizygotic pairs [see Gottesman and Shields (1976) for a discussion of concordance by pair or by proband].

Two of the concordant MZ pairs (1 and 3*) were closely similar in all respects. In each case, the twins were severely retarded and the autism was somewhat atypical.

*Numbers refer to case summaries in the Appendix.
in terms of the limited evidence of ritualistic features. However, in both the other two pairs, there were important differences between the twins in spite of concordance for autism. In one (2) there was an 18 point difference in non-verbal I.Q., and a 24 point difference in Peabody language quotient. The twin with a lower non-verbal I.Q. but higher verbal I.Q. made much more progress in both social relationships and use of language. In the fourth pair (4) there was a 39 point I.Q. difference; in this case, the more intelligent twin was less severely autistic, although the type of behaviour was closely similar in both. It is also notable that the more intelligent twin did not develop autism until 3 years of age, although apart from the late onset the clinical picture was typical of autism.

(b) Concordance for cognitive or social impairment

The next question is: what is inherited? Is it autism as such or is it some broader form of which autism is but one part? To answer this it is necessary to examine the pattern of disabilities in the non-autistic co-twins and to determine the concordance in MZ and DZ pairs for these disabilities.

In addition to the 25 autistic children, another six showed some form of cognitive impairment. In all cases, this involved some kind of speech or language deficit but the type of deficit varied. Three of the six children (cases 5, 8, and 12) had been markedly delayed in early speech development, not using phrase speech until 3 years or later. One of these (5) was also mildly retarded and attended a special school. A further child had markedly abnormal articulation to age 7 years, although she had not been delayed in early speech development. Another child (case 9) with SQ, of 70 had been generally mildly retarded in development and did not use phrase speech until 28 months. The sixth child (case 6) had a verbal I.Q. 21 points below the non-verbal and attended an ESN school but there had been no speech delay.

Five of the six children with cognitive impairment were in MZ pairs. Thus, five of the seven non-autistic children in MZ pairs had cognitive abnormalities compared with only one of the 10 non-autistic children in DZ pairs (Exact test; \( P = 0.0175 \)). As all the 25 autistic children also met the criteria for cognitive abnormality, the concordance rates may be recalculated for all forms of cognitive impairment, both autistic and non-autistic (see Table 4).

The results are striking. Nine of the 11 MZ pairs were concordant for some kind of cognitive disability, usually involving language, whereas this was so for only one out of the 10 DZ pairs (Exact test; \( P = 0.0015 \)).

Only one child (case 8), included in the six just mentioned, had social or behavioural problems at all reminiscent of autism, and he was diagnosed as showing autistic psychopathy on the basis of little social usage of speech, circumscribed interest patterns and a lack of social relationships.

Three of the other children with cognitive impairments, however, also showed some kind of social or emotional disability. One child (7) was painfully sensitive and self-conscious, crying over imagined slights; another (6) although friendly and sure of himself now, had had a severe and disabling dog phobia when younger, and a third (5) was rather shy, sensitive and lacking in confidence. A fourth child (13) without cognitive impairment developed a psychiatric disorder of uncertain nature at age 17 years. Because of the overlap with cognitive impairment, the concordance
in terms of social/emotional difficulties (including autism) is similar: eight out of 11 MZ pairs compared with two out of 10 DZ pairs.

(c) *Biological hazards and concordance*

The major difference in concordance between MZ and DZ pairs strongly suggests the importance of hereditary influences in the aetiology of autism. However, before drawing that conclusion it is necessary first to check whether the concordance patterns are explicable in terms of biological hazards associated with the birth process. We identified five features known to be associated with brain damage (and hence likely to predispose to autism): severe haemolytic disease (Gerver and Day 1950), a delay in breathing of at least 5 minutes after birth (Drage and Berendes, 1966; Hunter, 1968), neonatal convulsions (Rose and Lombroso, 1970), a second birth which was delayed by at least 30 minutes following the birth of the first twin (Dunn, 1965; Kurtz et al., 1955) and multiple congenital anomalies. Such features were present in 11 out of the 42 children.

<table>
<thead>
<tr>
<th>Biological hazards</th>
<th>Both twins</th>
<th>One twin only</th>
<th>Neither twin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Discordant</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 5 shows the concordance for autism in terms of biological hazards. In only two pairs, did both children experience biological hazards and both these pairs were discordant for autism. It may be concluded that the concordance is likely to be due to genetic factors and certainly is not explicable in terms of the perinatal complications on which we had data, and the same applies to the concordance for cognitive impairment. In none of the six pairs concordant for cognitive impairment but not autism were biological hazards present in both twins.

(d) *Biological hazards and discordance*

The next question is why only some of the children with a cognitive impairment showed the syndrome of autism. The possible importance of biological hazards in this connection was re-examined by focusing on the 17 pairs discordant for autism. In six of these pairs one, but only one, of the twins had experienced one of the five specified biological hazards. In all six cases, it was the autistic twin who was affected (see left-hand side of Table 6). However, there were a further 11 cases (see right-
hand side of Table 6) in which the biological hazards affected neither twin or both twins, and so did not account for the discordance.

**Table 7. Biological differences and discordance for autism**

<table>
<thead>
<tr>
<th>Biological differences</th>
<th>Autistic twin worse</th>
<th>Other twin worse</th>
<th>No difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ pairs</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

In order to examine these 11 discordant cases further, a wider definition of biological hazard, in terms of a marked difference between the twins, was employed. This included a birth weight at least a pound less than the other twin (three cases) (Willerman and Churchill, 1967), a pathologically narrow umbilical cord (one case), a more severe haemolytic anaemia associated with neonatal apnoea (two cases), and a severe febrile illness possibly involving encephalitis (one case). This differentiated a further six cases (see Table 7), and again it identified the autistic one each time. It may be concluded that some form of biological impairment, usually in the perinatal period, strongly predisposed to the development of autism. The pattern of findings is summarized in Table 8.

**Table 8. Summary of biological hazards in discordant pairs**

<table>
<thead>
<tr>
<th>Hazard</th>
<th>Autistic twin</th>
<th>Non-autistic twin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ PAIRS</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>Multiple congenital anomalies</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Neonatal convulsions</td>
<td>—</td>
</tr>
<tr>
<td>Possible</td>
<td>Severe febrile illness</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Pathologically narrow cord</td>
<td>—</td>
</tr>
<tr>
<td>None</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>DZ PAIRS</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>Apnoea</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Delay second birth</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Delay second birth</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Delay second birth</td>
<td>—</td>
</tr>
<tr>
<td>Possible or Difference in severity</td>
<td>Severe haemolytic disease + apnoea</td>
<td>Delay second birth</td>
</tr>
<tr>
<td></td>
<td>Severe haemolytic disease + apnoea</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Birth weight 1½ lb lower</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Birth weight 1½ lb lower</td>
<td>—</td>
</tr>
<tr>
<td>None</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Did the same biological hazards explain the presence of a cognitive deficit? To examine this question, we compared the six non-autistic twins who showed
cognitive impairment with the 11 non-autistic twins without a cognitive deficit. The only two children (out of these 17) who had experienced a biological hazard were both without a cognitive disability. Clearly, biological hazards did not account for the presence of cognitive abnormalities.

(e) *Psychosocial influences*

The final issue was whether psychosocial environmental influences were associated with discordance in terms of either autism or cognitive impairment. Because both were evident from early life, it was necessary to focus on possible factors in the infancy period, which meant that our data were necessarily retrospective in large part and often crude. All pairs had been reared together during infancy, although in one case (11) the autistic child was often in hospital during the first year. In this case, the severe early lack of responsiveness was followed by maternal rejection. There were no differences between the autistic and non-autistic children in experiences other than those which were associated with the greater frequency of neonatal biological hazards. Thus, out of the nine cases in which there was a difference in time before discharge home after birth, in seven it was the autistic child who stayed in hospital longer. In some instances, this involved periods in an incubator or some kind of intensive care.

**DISCUSSION**

(a) *Sampling and selection*

Before discussing the meaning of the findings it is necessary to consider the adequacy of our sampling, as the rest of the results hinge on that. In order to obtain as complete a sample as possible we used an unusually large number of sources of diverse kinds. As a result, most of the children were reported by several different agencies. This in itself provides some indication of the efficiency of our sampling techniques. However, two better checks are available. First, there is the monozygotic-dizygotic pair ratio. For same-sexed pairs surviving the first year, the ratio should be approximately 6 : 7 (Slater and Cowie, 1971), which is very close to our observed ratio of 11 : 10. Second, there is the number of autistic children found. The Registrar-General figures for 1964 show that 6176 liveborn same-sexed twins were born that year (Slater and Cowie, 1971). Taking a 1-year survival rate of 88.1% (based on Gittelsohn and Milham’s 1965 figures) that reduces to 5441. Our sampling was most thorough for the school years so if we multiply that by 13 to obtain the figure for the birth years 1958–1970 that makes 70,733 pairs and 141,466 children. The next step is to calculate the proportion of autistic children expected. We had to rely on information about children referred to clinics or special schools and diagnosed as autistic by them and later also by us. For this purpose, the administrative surveys probably provide the most appropriate initial guide. In Britain, the Department of Education figures showed a prevalence of 1.75 per 10,000 (Wing et al., 1976) and in the U.S.A. Treffert’s (1970) figure was 2.5 per 10,000. On this basis, we should have had between 24.8 and 35.4 children. However, as with other studies (Wing et al., 1976), we found that not all the cases reported as autistic met our diagnostic criteria. In practice, we excluded about a quarter, which brings the expected number of twins in our final
sample down to 18-6 to 26-6.* In fact (excluding the four children born before 1958 and the one living in Scotland) we obtained 20 autistic children who were part of a same-sexed pair—which is very close to the expected number. It may be concluded that there is every reason to believe that our sample of autistic twins was about as complete as it could be.

It is also necessary to consider whether the choice of a twin sample introduced any particular biases. The most obvious possibility concerns the frequency of perinatal complications. These tend to be rather commoner in multiple births than in single births (Dunn, 1965) and this may have increased the likelihood of our finding an association between birth hazards and autism. On the other hand, studies of singletons have also suggested that perinatal complications tend to be somewhat commoner in autistic children than in other children (see e.g. Lotter, 1967; Whittam et al., 1966; Hinton, 1963; Moore, 1972; Knobloch and Pasamanick, 1974; Torrey et al., 1975), although not usually to the extent found in this twin sample. It should be noted, however, that our sample did not have particularly low birth weights. Thirty of the 42 children had a birth weight of over 5 lb and none had a birth weight under 3 lb. We may conclude that our choice of a twin sample probably increased the likelihood of finding an association between perinatal complications and autism, but similar associations of lesser degree have been noted in singletons.

Similarly, it is well known that delayed acquisition of speech is commoner in twins than singletons. It might be suggested that this is why so many of the non-autistic twins showed impaired language. However, were this simply due to twinning, it would be expected to occur with equal frequency in the MZ and DZ pairs (Mittler, 1971). In fact, we found that abnormalities of language were much more frequent in the MZ than in the DZ twins. Moreover, the abnormalities we found did not consist of just speech delay but rather involved a wider range of cognitive functions.

Finally, there is the question of sample size. How much confidence can be placed on the MZ–DZ differences in concordance in view of the relatively small sample size of 21 pairs? Obviously, some caution is needed before drawing too sweeping conclusions, and clearly replication is required. Nevertheless, as already indicated, there are good reasons for supposing that this twin study has avoided the serious biases which plague twin research. Moreover, although the sample is small, the MZ–DZ differences were large and statistically significant. It seems likely that the concordance differences are true ones.

(b) Hereditary influences

The MZ–DZ difference in concordance for autism and the much larger difference in concordance for cognitive disorder clearly points strongly to the importance of genetic factors in the aetiology of autism. Indeed, the size of the MZ–DZ difference, together with the population frequency of autism indicate a very high heritability or coefficient of genetic determination (Smith, 1974; Curnow and Smith, 1975). The finding that concordance is strongly associated with the zygosity of the twin pairs

*However, using Lotter's (1966) true prevalence figures and also a broader definition of autism than we employed, there should be 63 autistic twins in the country who could be identified by means of a population survey.
and not at all with the presence of physical environmental hazards indicates that
the concordance truly represents an hereditary influence rather than biological
damage during the birth process. In this connection, it should be noted that there
are greater intra-uterine environment differences in MZ than in DZ pairs, as re-
lected, for example, in the greater mean difference in birth weights in MZ pairs
(Mittler, 1971).

(c) What is inherited?

The findings clearly point to the conclusion that the hereditary influences are
concerned with a variety of cognitive abnormalities and not just with autism. In
other words, autism is genetically linked with a broader range of cognitive disorders.
The results also show that the cognitive deficits linked with autism usually involve
delays or disorders in the acquisition of spoken language. Thus, of the six pairs
concordant for cognitive impairment, in three the non-autistic twin was not using
phrase speech until after his third birthday. One of the remaining three showed a
lesser degree of speech delay, a second had verbal skills much inferior to visuo-spatial,
and the third had very abnormal articulation. It may be inferred that language
difficulties of some kind are generally part of the problem. The conclusion is in
keeping with the extensive evidence for the importance of abnormalities in language
and symbolization in autism (Rutter, 1974).

On the other hand, in most of the non-autistic children, it was not usually a
straightforward isolated developmental delay in language acquisition. First, two of
the six children also had some general intellectual impairment. Second, in one case,
the language delay involved echolalia, and in another it involved a lack of social
usage comparable to that found in infantile autism. It seems that a language deficit
may be a part of the cognitive impairment in most cases but it is not usually a
“pure” or isolated delay in the acquisition of spoken language. Of course, it is not
suggested that all forms of language impairment are genetically linked to autism.
Indeed, in most respects, the language characteristics of autistic children are very
different to those of children with a developmental language disorder (Bartak
et al., 1975, 1977). However, it seems that some cases of language abnormality are genetically
linked with autism. Unfortunately, knowledge is lacking on how to tell which
these are.

It is also necessary to ask whether the social and emotional difficulties which
were present in most of the children with a cognitive deficit are also part of what is
inherited. For several reasons, no firm conclusions are possible on this point. In the
first place, social difficulties and emotional disturbance are quite common in any
group of children with language delay (Rutter, 1972; Stevenson and Richman,
1977), and with a sample as small as ours it was not possible to determine whether
difficulties were more common in this group. In the second place, only one of the
six children with cognitive impairment had social difficulties of a kind at all similar
to those shown by autistic children. It may be that the shyness, fears and sensitivity
are part of what is inherited or it may be that, as in other children with language
delay, they are merely temporary secondary emotional reactions to cognitive and
communication difficulties. The present data do not allow a choice between these
two possibilities.
A twin study could provide the opportunity to examine possible links between autism and schizophrenia. However, very few of the twins in this sample were old enough to determine whether autism and schizophrenia ever occur together in monozygotic pairs. None of the monozygotic twins had a disorder with any resemblance to schizophrenia. But there was one non-autistic dizygotic twin who showed social withdrawal at age 17 years. The possibility of schizophrenia clearly arises, but there was no evidence of thought disorder, delusions, hallucinations or any other first rank symptoms. Further follow-up is needed to make a diagnosis. Nevertheless, it should be added that, in spite of a large number of twin studies of schizophrenia, no case has ever been reported of infantile autism occurring in a non-schizophrenic co-twin.

(d) Mode of inheritance

It is obvious from the low rate of disorder in the sibs that autism is not a disease inherited in clear-cut Mendelian fashion. However, many factors (e.g. phenocopies, genetic heterogeneity, incomplete penetrance, high mutation rate, etc.) may distort the simple Mendelian ratios. In practice, it is extremely difficult on the basis of family data to differentiate between monogenic inheritance with incomplete penetrance and polygenic or multifactorial effects (Curnow and Smith, 1975). In the case of autism, the sorting out of mode of inheritance is much complicated by the fact that autistic children rarely marry and have children. One crucial piece of information which is needed is what happens to the offspring of non-autistic sibs or twins with cognitive impairment. Unfortunately, no information is available on that point and until this is known genetic model building seems premature.

(e) Environmental influences

Our findings clearly indicate that, in addition to hereditary factors, environmental hazards involving the risk of brain damage also play an important part in the aetiology of autism. Out of the 17 pairs discordant for autism, there were 12 in which autism was associated with some kind of biological hazard or difference which affected the autistic child and not his co-twin. In this series, with one exception, the biological features were all perinatal in origin. However, it is clear from studies of non-twin samples that autism may arise on the basis of quite diverse forms of brain pathology, including congenital rubella (Chess et al., 1971) and infantile spasms (Taft and Cohen, 1971).

Although both hereditary and environmental influences play an important part in the genesis of autism, the findings from this study suggest that they work in rather different ways. The MZ–DZ concordance differences showed that the hereditary factor(s) were concerned with the genesis of cognitive/linguistic abnormalities rather than with just autism as such. But this was not the case with the biological hazards at all. They were completely unassociated with non-autistic cognitive deficits in spite of a strong association with autism.

(f) Genetic–environmental interactions

That difference raises the question of how far hereditary and environmental influences cause different cases of autism and how far they act in conjunction as part
of a multifactorial determination. Our data do not allow any firm conclusions on this point but they suggest that both occur.

The four MZ pairs concordant for autism suggest that, in some cases, genetic factors may be sufficient to cause autism. Only one of the eight autistic children in these four pairs suffered a hazard at all likely to lead to brain injury—his disorder was more severe than that of his co-twin.

On the other hand, it appears that brain injury alone may also be a sufficient cause of autism. This is suggested by the fact that biological hazards occurred with much the same frequency in MZ and DZ pairs. It is also indicated by the finding from other studies that the rate of autism in children with particular forms of brain pathology, such as caused by congenital rubella (Chess et al., 1971) is considerably higher than that in the sibs of autistic children.

Nevertheless, many cases of autism appear to result from a combination of brain damage and an inherited cognitive abnormality. This is suggested by the finding that out of the seven MZ pairs discordant for autism, in four cases the autistic child but not his non-autistic co-twin had experienced some form of biological hazard liable to cause brain damage. In three of these four cases the non-autistic child had a cognitive deficit, suggesting that it may have been brain injury that converted the deficit into a full-blown autistic syndrome.

In this regard it is interesting that, over a decade ago, van Krevelen (1963) suggested that autism might result from the combination of an inherited personality deficit plus organic brain damage. The present results are in accord with that general hypothesis, but the deficit found involved cognitive/linguistic abnormalities rather than the “autistic psychopathy” syndrome postulated by van Krevelen.

In summary, we may conclude that this systematic study of 21 same-sexed twin pairs in which at least one twin showed the syndrome of infantile autism indicates the importance of a genetic factor which probably concerns a cognitive deficit involving language. It also indicates the importance of biological hazards in the perinatal period which may operate either on their own or in combination with a genetic predisposition. However, uncertainty remains on both the mode of inheritance and exactly what it is which is inherited.

SUMMARY

A systematic study was made of a representative group of 21 same-sexed twin pairs (11 MZ and 10 DZ) in which at least one twin showed the syndrome of infantile autism. There was a 36 per cent pair-wise concordance rate for autism in MZ pairs compared with 0 per cent concordance in DZ pairs. The concordance for cognitive abnormalities was 82 per cent in MZ pairs and 10 per cent in DZ pairs. It was concluded that there were important hereditary influences concerning a cognitive deficit which included but was not restricted to autism. In 12 out of 17 pairs discordant for autism, the presence of autism was associated with a biological hazard liable to cause brain damage. It was concluded that brain injury in the infancy period may lead to autism on its own or in combination with a genetic predisposition. Uncertainty remains on both the mode of inheritance and exactly what is inherited.

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APPENDIX: CASE SUMMARIES OF CASES

MONOZYGOTIC PAIRS

**Case 1**


**Family.** Fa. is industrial engineer. Mo. had one episode untrtd. depression. Three older sibs: two had single episodes of severe depression.

**Pregn.** Hyperemesis and fainting throughout. Gestation 36 weeks.


**Case 2**


**Family.** Fa. is plumber (born W. Indies), was late talking. Mo. anxious and recurrently depressed (untrtd.). Two sibs. (one older, one younger), one behav. diffs. at school.

**Pregn.** Anaemia, transfusion. Gestation 40 weeks.


Case 3
Zygosity determined b/d. grps. Pair concordant for (atypical) autism. Male. Age 14 yr.
Family. Fa. is porter. Mo. nurse. Four older sisters.
Pregn. normal, 34 weeks, gestation. 24 hr labour.


Case 4
Zygosity determined b/d. grps. Pair concordant for autism (one atypical). Male. Age 8 yr.
Family. Fa. univ. teacher. Mo. had one previous pregn.—terminated because hydramnios. Bilingual family.
Pregn. Vomiting early months. Pre- eclamptic toxaeemia. Induced 39 weeks.


Case 5
Zygosity determined b/d. grps. Pair discordant for autism, concordant for cognitive and social/ emotional disorder. Female. Age 15 yr.
INFANTILE AUTISM: A GENETIC STUDY OF 21 TWIN PAIRS

Family. Fa. engineer (univ. grad.). One normal older sister. Mo. also had one still birth at 7 months.

Pregn. Bleeding at 2 months. 39 week gestation. Twins not diag. and delivery at home.


Case 6

Family. Fa. tradesman. One normal older sister. Mo. also had one still birth.

Pregn. Severe vomiting first trimester. Toxaemia last trimester; 2 admissions. 39 week gestation.


Case 7
Zygosity determined bld. grps. Pair discordant for (atypical) autism, concordant for cognitive and social/emotional disorder. Female. Age 12 yr.


Pregn. Bleeding at 3 and 4 months. 35 week gestation.


2nd born twin. Breech. B. wt. 5 lb 4 oz. In hosp. 14 days. Normal neonatal course. Normal motor milestones. Single words 2 yr. Normal develop. apart from immature speech and poor articulation until 4½ yr when had severe febrile illness and profound change in behav. Lost social responsiveness, marked reduction in speech, eating poor, appeared aimless, ceased to play. Until 6 yr lack of personal

Case 8
Zygosity determined dermatoglyphics and appearance. Pair discordant for autism, concordant for cognitive and social/emotional disorder. Male. Age 10 yr.

Family. Fa. business manager. One younger sister (4 yr) with echoing and poor articulation. Lines up objects. Normal social relationships and normal social usage language. Having psychiat. trt. for encopresis. There are several eccentrics in mo.'s family.


Case 9
Zygosity determined bld. grps. Pair discordant for autism, concordant for cognitive disorder. Female. Age 5 yr.

Family. Fa. street trader. Mo. I.P. 9 months for depression following misc. Nine older sibs and one younger. Mo. also had three misc.

Pregn. 34 wk gestation.


Case 10
Zygosity determined bld. grps. Discordant pair (atypical autism). Male. 7 yr.

Family. Fa. accountant: late in speaking, said little before starting school. Odd personality. Mo.
trtd. as I.P. for depression. Older bro. did not speak until 2½ yr. Socially awkward and no friends until 6 yr. Interested in maps and routes. Mo. also had one misc.

_Pregn._ Normal. 39 week gestation.


**Case 11**

Zygosity determined by dermatoglypics. Discordant pair. Male 9 yr.

_Family._ Fa. business manager. Three older and one younger normal sibs. Parents divorced.

_Pregn._ 34 week gestation. Mo. ill in bed most of pregnancy.


2nd born twin. B. wt. 4 lb 1 oz. One neonatal convulsion. In incubator 1 week. Thrived poorly and persistent feeding difficulties. Left hosp. 6 weeks after birth but readmitted twice during next 18 months. Unresponsive difficult baby, did not smile and did not want to be held. Lack of eye to eye gaze. Mother very distressed by difficulties and after a while could not bear to deal with child; no relationship with parents until after 6 yr. Lack of sympathy. Now beginning to play with peers. Good fine motor coordination but did not walk until 2½ yr. Lack of babble. Single words after 2 yr; phrase speech 3 yr 10 months. Early echolalia and stereotyped phrases. Little social speech; poor abstraction and conceptualization. Counting rituals when younger. Follows routines. Repetitive stereotyped drawings. In psychiat hosp. age 2–5 yr. Since lived with father. Now attends normal school. I.Q. Biret 100. S.Q. 80. Mecham L.Q. 81. Manneristic gait; otherwise neurol. N.A.D.

**DIZYGOTIC PAIRS**

**Case 12**

Zygosity on bld. grps. Pair discordant for autism, concordant for cognitive disorder. Male. 5 yr.

_Family._ Fa. accountant; rather obsessive personality, no social life. Two paternal uncles with definite social oddities; without friends, unusual circumscribed interests, unmarried, fastidious and precise. Normal older sister. Older bro. now normal but ? late in onset of speech, also head banging and resistance to change as baby.

_Pregn._ High B.P. Mo. I.P. x 3 for rest. 39 week gestation. Mo. is Rh neg. but no antibodies.

1st born twin. B. wt. 5 lb 12 oz. Dysmature appearance. Bilirubin rose to 10 mg. In special care unit. Lowest bld. sugar was 36 mg %. Motor milestones delayed. Walked 23 months. Lack of respon-

Case 13
Zygosity on marked diffs. appearance. Pair discordant for (atypical) autism, concordant for social/emotional disorder. Male. 18 yr.


2nd born twin. B. wt. 8 lb. Rectal abscess at 6 weeks. Normal neonatal course. Normal motor milestones. Normal social and emotional develop. Did well at school. Passed 'O' levels at 16 yr. At 17 yr gradually stopped attending school, kept to his room, refused to get job. Surly and unpleasant to family. Held job for short while. Accepted at several colleges but attended courses for few days only. Spends time lying in bed reading about cybernetics and listening to music. WISC I.Q. VS 108. PS 131. Normal social maturity. Normal language. No thought disorder, delusions or hallucinations.

Case 14

Family. Fa. farm owner. Anxious man prone to depression (not trtd.). Mo. slow to talk and reading diffs. until 10 yr. Two younger sisters, both of whom had exchange transfusions; one having psychiat. trt. (no details).


Case 15
Zygosity on basis of marked diffs. appearance. Discordant pair. Male. 16 yr.

Family. Fa. draughtsman. No sibs.

Pregn. Toxaemia. 36 week gestation.

1st born twin. B. wt. 4 lb. In incubator 10 days. In hosp. 30 days eye infection. Vomited and cried in first months. Slow feeder. Normal motor milestones. Lack of eye to eye gaze and failure to cuddle


Case 16
Zygosity on basis of marked physical diffs. Discordant pair. Male. 22 yr.
Family. Fa. teacher. Two older and one younger sib—all normal and above av. intelligence.
Pregn. 34 week gestation. Prolonged labour.

Case 17
Zygosity on basis of marked physical diffs. Also probably diff. bld. grps. (because only one twin had erythroblastosis foetalis). Discordant pair. Male. 13 yr.
Family. Fa. electrician (born West Indies). Three older children all normal and of above av. attainment (two passed 'O' levels and third not yet at that age). Mo. occ. depressed (not tretd.).
Pregn. Mo. Rhesus neg. with antibodies. 33 week gestation.

Case 18
Zygosity determined bld. grps. Discordant pair. Female, 12 yr.
**Family.** Fa. factory foreman. Two older bros. both psychiat. normal but one had tutoring for reading diffs.

**Pregn.** Normal 40 week gestation.


**Case 19**

Zygosity on basis marked physical diffs. Pair discordant (atypical autism). Female. Age 14 yr.

**Family.** Fa. printer. Died when twins 10 yr. Two older bros.; one autistic and mentally retarded (not seen but no speech, lack of eye to eye contact, hand and finger mannerisms and attachment to unusual objects). Strong F.H. on father’s side of severe myopia.

**Pregn.** Severe vomiting first trimester. 40 week gestation.


**Case 20**

Zygosity on basis marked physical diffs. Pair discordant. Male. 6 yr.

**Family.** Fa. artist. Mo. had Psychiat. trt. for emotional dist. One normal younger sib.

**Pregn.** Normal. 36 week gestation.


INFANTILE AUTISM: A GENETIC STUDY OF 21 TWIN PAIRS

Case 21

Zygosity on basis diffs. in appearance. Pair discordant. Female. 20 yr. Extensive info. from case notes and other reports but family not seen.

Family. Fa. salesman with recurrent manic-depressive illness.

Pregn. Severe vomiting first trimester. 34 week gestation.

1st born twin. B. wt. 5 lb 6 oz. Normal neonatal course. Shy and anxious at time of Fa.'s illness but otherwise a friendly sociable girl with many friends. No behaviour diffs. Above av. attainment. Currently a univ. student.


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INFANTILE AUTISM: A GENETIC STUDY OF 21 TWIN PAIRS 321


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