Comments on Autism Research Themes – Eileen Nicole Simon

Heterogeneity – p 2

Autism is associated with many different medical conditions. Idiopathic autism is not necessarily the result of some yet to be identified genetic cause. Environmental causes must be sought for the recent increased prevalence of autism. Phenylketonuria (PKU) was a genetic cause of autism in the past. Note that discovery of the metabolic defect in PKU, and treatment by dietary restriction of phenylalanine, predate discovery of the structure of DNA.

A final common pathway in the brain? – p 3

Developmental language disorder is the core handicap of children with autism. The brain impairment underlying this handicap is the final common pathway of all etiologies of autism. The auditory system is metabolically the most active system in the brain, and is vulnerable to all the known factors associated with autism. Children normally learn to speak “by ear” and impairments in auditory function should be sought as the cause of developmental language disorder.

Predispositions and environmental factors – p 5

Predispositions for autism need not be genetic. Almost all infants are subjected to invasive obstetric procedures and neonatal treatments. Clamping of the umbilical cord, vaccinations, and antibiotic treatments do not cause apparent harm to most infants, but infants unlucky enough to suffer ischemic impairment of the auditory system (by clamping off postnatal placental blood flow too soon) may be at greater risk for injury from postnatal treatments.

Research with twins – p 8

Twins are at greater risk for perinatal compromise, and this needs to be considered when trying to determine why only one of identical twin pairs may be afflicted with autism.

Twin case studies – p 8

Rosanoff et al. (1934) and Folstein & Rutter (1977) provide case reports of autism in identical and fraternal twins that point to the importance of perinatal problems as a cause of autism.

Summary of the paper by Rosanoff et al. (1934) – p 12
**Heterogeneity**

Heterogeneity of the many metabolic disorders associated with autism implies a “final common pathway” in the brain that is affected by all. Prenatal exposure to substances like alcohol or valproic acid must also affect the same common pathway.

Note:

1. Phenylketonuria (PKU) is a metabolic disorder associated with autism [1,2]. Newborn screening and subsequent restriction of phenylalanine in the diet has removed this condition as a common cause of autism or developmental disabilities.

2. An abnormal metabolite, phenylpyruvic acid, was discovered in the urine of two children by Asbjørn Følling in 1934 [3, 4]. Within 20 years phenylpyruvic acid was found to be an abnormal metabolite produced by a defective enzyme in the liver (not the brain) of children with PKU [5, 6].

3. The cause and treatment for PKU was worked out before the structure of DNA was determined [7]. Subsequent discovery of genetic variants of PKU provides insight into the nature of metabolic disorders, and provides a framework for investigating genetic mechanisms that lead to metabolic abnormalities [8].

Knowing the abnormal metabolites that are toxic to the brain is more important than knowing the mutations for coming to understand how the developing brain is affected and what the final common pathway is of autism’s multiple etiologies [9].

**References**


A final common pathway in the brain?

The final common pathway in the brain must be responsible for the core handicaps of children with autism. The most serious handicap is developmental language disorder. Most children learn to speak “by ear” and because children with autism are often hypersensitive to noise, an auditory disturbance that interferes with learning to speak should be sought.

Children with autism often exhibit “delayed echolalia” using phrase fragments out of context. Kanner (1946) referred to this as “irrelevant and metaphorical language” or language that at best is tangential to context [1]. Children with autism often display the ability to commit a large amount of verbal information to memory. They are often also very musical. These features of the disorder provide evidence of an excellent (unimpaired) memory. They clearly hear and retain the musical envelope of speech.

What children with autism fail to hear are the distinctive features of words (and syllables) that should evoke associations with having heard these words in their great store of remembered phrases. Rapin (1997) suggested that some children with autism may suffer from a “verbal auditory agnosia” or an inability to hear the boundaries between words and syllables [2].

Evidence is available indicating where in the auditory system such a defect might be located. Since the development of MRI, at least 13 cases of “verbal auditory agnosia” have been reported in people who suffered bilateral injury of the inferior colliculi [3-14].

Evidence has been available for 50 years that ischemic damage of the inferior colliculi occurs following asphyxia at birth [15]. The inferior colliculi have the highest rate of blood flow and aerobic metabolism in the brain [16-18]. Evidence has been available for more than 100 years that the inferior colliculi are vulnerable to damage by factors that impair aerobic metabolism in a pattern of neuropathology known as Wernicke’s encephalopathy [19-30].

Measures of auditory system dysfunction using EEG evoked potentials or structural and functional MRI should be a focus of research. Refinement of these research techniques should always be sought.

References
Predispositions and environmental factors

What is a predisposition? Belonging to the human race is a predisposition for language disorders. Any factor that impairs hearing or the language circuits of the temporal and frontal lobes is a predisposition for language disorder in humans.

Children normally learn to speak before the language circuits of the temporal and frontal lobes are fully mature. Children learn to speak “by ear” through hearing, and any abnormality in hearing should be considered a predisposition to developmental language disorder.

It is common knowledge (gained by universal observation) that children with autism are hypersensitive to certain sounds – the ringing of a telephone, vacuum cleaners, echoes in a gymnasium or school cafeteria, and more.

Inhibitory neurotransmission in the auditory system should be investigated as a possible reason for this hypersensitivity. Researchers in the field of auditory processing should be recruited to investigate hyperacusis in children with autism. Serotonin and/or gamma-aminobutyric acid (GABA) may be neurotransmitters that normally damp repetitive firing of excitatory neurons after onset of ongoing sounds that should be perceived as background noise.

Neurotransmitters (like somatostatin and leu-enkephalin) appear during early development, then disappear. These and more yet-to-be-discovered timed factors may guide maturation of

neural pathways in the language areas of the temporal and frontal lobes. Injury within the auditory system needs to be investigated as serious consequence of any lapse in respiration during or immediately following birth.

It seems no one wants to question the increasingly invasive procedures used in obstetrics or neonatal care. However any newborn requiring resuscitation should be followed into the early school years for any signs of language delay or dyslexia. Are induction of labor or planned cesarean delivery safe? Is it safe to suddenly clamp off ongoing placental respiration following birth? Where is the evidence? None of the randomized-controlled-trials (RCTs) makes any comparisons with natural birth, with no use of a clamp, and none follow development beyond observations made in the neonatal nursery.

The auditory system is the most metabolically active system in the brain, and it is vulnerable to ischemic damage [1-3]. Blood flow to and from the placenta continues, often for several minutes if not stopped by use of a clamp [4]. Ongoing placental blood flow is intended to fill the capillaries that supply the alveoli [5]. If ongoing placental blood flow is clamped off, blood to fill the alveolar capillary bed will be drawn from other body organs. If blood from the brain goes to the lungs at birth, the auditory system is likely to suffer damage.

The published protocol for clamping the umbilical cord as soon as possible after birth should be investigated as a possible reason for increasing prevalence of autism and other childhood problems like asthma, patent ductus arteriosus, and more [6].

Ischemic injury of the auditory system could at this point in time be considered a predisposition (because of the universal practice of umbilical cord clamping). Environmental factors that could then exacerbate “minor” impairment of the auditory system might then be neonatal vaccinations or antibiotics.

Kernicterus (bilirubin staining of subcortical nuclei) was shown long ago to follow an ischemic insult [7-9]. The picture below (following the references) from the paper by Lucey et al. (1964) revealed that bilirubin staining is not uniform throughout the brain. Likewise any unnatural environmental substance like vaccine components or antibiotics are likely to selectively affect brain nuclei compromised by ischemic injury during birth.

Umbilical cord clamping does not cause injury to most infants (the lucky ones), and likewise vaccination, antibiotics and other treatments do not injure most infants. The unlucky few who suffer ischemic injury, then are immediately vaccinated or treated for infection may then suffer the lifelong affliction of autism or other developmental disabilities.

References
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Note: Bilirubin staining occurred only in subcortical nuclei of high metabolism and blood flow - like the inferior colliculi of the midbrain auditory pathway (lower left).
Research with twins

Autism is not 100 percent concordant in identical twins, which means it is not the result of a single defective gene [1]. The finding of even one pair of identical twins who are discordant for any disorder provides the counterexample that disproves a single gene etiology. Greenberg et al. (2001) noted a higher concordance of autism in fraternal twins than would be expected in the general population, which should indicate that environmental influences are more significant than genetic factors [2]. If environmental factors were not involved, the concordance rate for fraternal twins should not be greater than between single-born siblings in families in which autism has occurred more than once.

Norman (1982) noted that perinatal hazards are increased for twins and suggested that therefore twins are an imperfect model for genetic versus environmental studies of things like intelligence [3]. That concordance is higher in identical than fraternal twins reflects factors such as the limited capacity of a shared placenta to withstand environmental hazards like anoxia or prenatal infections. Davis et al. (1995) found that twins who both develop schizophrenia were more likely to have shared a single placenta and chorionic sack in utero [4]. Autism becomes evident years earlier than schizophrenic disorders and is therefore even more likely related to perinatal environment. Of the identical twins studied by Belmonte and Carper (2006), the more seriously affected twin was not breathing at birth [1]. Further, he failed a hearing test at 9 months of age, which was the impetus for the parents seeking advice, and suggests that auditory system impairment might be related to not breathing at birth.

References


Twin case studies

The article by Rosanoff et al. (1934) on the etiology of so-called schizophrenic psychoses is one of a series of reports on investigations of twins. Among 1014 twin pairs, cases of dementia praecox (schizophrenia) were identified in 142 subjects. In the 19 male pairs and 22 female pairs of monozygotic twins, both twins were affected in 10 of the male pairs and 18 of the
female pairs. The total concordance rate was 68.3 percent, but in female pairs it was 82 percent and in male pairs only 53 percent.

In 11 pairs of dizygotic twins where both were male, three (27 percent) both developed schizophrenia. In 42 dizygotic female pairs, seven (17 percent) were both affected. Among 48 pairs of opposite sex twins, five were both affected. Pairs in which only one twin became schizophrenic, 21 were males and 22 females. Total concordance rate in dizygotic twins was 14.9 percent. Rosanoff et al. cited Humm's (1932) concordance rate of 3.1 percent among siblings of schizophrenic patients, and concluded that the excess among dizygotic twin pairs must be attributed to factors other than heredity.

Rosanoff et al. observed that hereditary factors were not always present, and therefore not essential, in the etiology of schizophrenic psychoses. They found similarity of psychotic manifestations in both of a pair of monozygotic twins was the exception rather than the rule, and suggested that though hereditary factors seemed to play an important part their pathogenic effects were not specific.

A more detailed scrutiny revealed the possibility of separating out a group of cases that occurred on a basis of “partial decerebration” of traumatic or infectious origin. In support of this Rosanoff et al. pointed out that at least five, of the nine monozygotic male pairs in which only one was affected, had clear-cut evidence of trauma or infection affecting the central nervous system – one of these was a victim of the influenza epidemic of 1918-1919. They found the proportion of cases with traumatic or infectious etiology to be higher in males than females, and suggested a more marked cerebral vulnerability in males.

Birth trauma was cited by Rosanoff et al. as a probable cause of “partial decerebration.” They stressed that slight, unnoticed, and even unnoticeable traumas were capable of producing decerebration syndromes that would be manifest only after twenty years or more. In support of this was the delay after trauma, producing unconsciousness in childhood, in some of those who later developed schizophrenia.

Folstein and Rutter (1977) investigated cases of autism occurring in twins. Eleven pairs were identical (monozygotic), and ten fraternal (dizygotic). Concordance for autism was found in 4 of the 11 pairs of monozygotic twins (36 percent) and no concordance was found in the dizygotic pairs. Thus of 21 twin pairs, 17 were discordant for autism and in 12 of these autism was associated with an event likely to cause brain damage. A genetic predisposition was nevertheless postulated as possibly contributive.

Concordance for non-autistic cognitive abnormalities was found in 5 of the 11 monozygotic twin pairs; thus 9 of 11 (82 percent) of the monozygotic pairs were concordant for developmental disabilities of one kind or another. Concordance for cognitive disorder was found in only one of the dizygotic twin pairs.
Most useful in the paper by Folstein and Rutter are the case reports. Of the monozygotic twin pairs concordant for autism, all four are male and complications of pregnancy were noted in each case:

(1) The mother of the first pair had hyperemesis and fainting spells throughout pregnancy. The twins are noted (at age 22) to be concordant for atypical autism. One was described as having poor coordination and awkward gait, the other better coordinated and with normal gait; but the second twin developed seizure disorder at age 16.

(2) Mother of the second pair had a transfusion for anemia during pregnancy. The twins were both echolalic and had poor gross motor coordination. Both learned to read but at age-levels 3 to 4 years younger. The second-born twin began using speech appropriately at age 10, and at age 12 was described as friendly with adults but with no peer friendships.

(3) Mother of the third pair went into labor of 24 hours duration after 34 weeks gestation (six weeks early), and each twin was a breech birth; one weighed 5 lb 10 oz, the other 5lb 4 oz. The twins are described (at age 14) as concordant for atypical autism, with wrist biting, restlessness, poor coordination, wide-based gait, and strabismus. Both developed lead poisoning from pica and the second-born twin had suffered a recent major epileptic fit with social deterioration.

(4) Labor was induced at 39 weeks gestation in the fourth mother because of pre-eclamptic toxemia; low forceps were used to deliver the first twin, the second born 30 minutes later due to uterine inertia suffered fetal distress, required positive pressure oxygen, and breathed only after 7 minutes. Autism and cognitive disability of this second twin are more severe than in his brother. The first-born twin at age 8 was attending a normal school, with IQ scores within the normal range. The second-born twin at age 8 still had language skills less than an 18-month level.

The differences are striking in the above cases, which were the four twin pairs deemed concordant for autism. The first and third pairs were described as atypical autism. One of the fourth pair was viewed as atypical, but the second-born twin who did not breath until 7 minutes after birth can be seen from the account given to be far more severely impaired than his identical twin brother.

Three of the five identical twins discordant for autism but concordant for other cognitive or social/emotional disorder are female. Mothers of two of the female pairs and one of the male pairs had bleeding during the early months of pregnancy; one had hydramnios, another toxemia during the third trimester. Delivery of male twins was by forceps in the mother with hydramnios because of uterine inertia; one twin had a cleft palate, no physical deformities were reported in the non-autistic twin. The autistic twin with cleft palate was born in a face presentation. One female infant who became autistic was a breech birth with delayed breathing; her umbilical cord was described as very narrow and white.
The non-autistic twins with other cognitive or social/emotional disorders are as different from each other as from their autistic identical twin. Two are in normal schools (at ages 5 and 12). One receives special tutoring in reading and is the twin of the child with cleft lip; questionable autistic psychopathy is noted in his case although he is described as friendly but shy. A third non-autistic twin (age 15) was in a normal school until age 11.

Features that distinguished autistic from non-autistic twins included lack of eye to eye gaze, blank facial expression, mannerisms, no play with peers, and echolalic speech. One female twin became autistic after a severe febrile illness at age 4 and ½ with a profound change in behavior. Up to that point, she appeared healthier than her twin sister had.

One of the autistic twins of the two discordant pairs appeared to be developing normally until deterioration of speech, lack of response to sounds, and loss of emotional response occurred at age 3. Both of the discordant pairs were male. The normal twins of the discordant pairs were (at ages 7 and 9) in normal schools with IQ scores in the normal range and with normal peer relationships.

Of the dizygotic twin pairs, three of the mothers were Rh-negative. The three twin pairs of these mothers were all male. The only twins concordant for cognitive disorder were born to one of these mothers; she did not have Rh-factor antibodies but bilirubin rose to 10 mg in the neonatal period of the twin who became autistic. Exchange transfusions were performed in both twins of one Rh-negative mother. Of the third Rh-negative mother, only the twin who later became autistic had an exchange transfusion at birth.

The mother of one of the dizygotic twin pairs had obstructed labor lasting 24 hours, and Caesarian delivery was performed after a failed attempt with forceps. The first born of this pair became autistic. The second-born twin of three mothers with uterine inertia became autistic. Two were female infants, born 30 and 45 minutes after delivery of their twin sisters who developed normally. One was a male infant born 75 minutes after his brother who also developed normally.

Overall, it would seem hard to question the role of perinatal compromise in all of the infants in this study. The most obvious genetic predisposition is the occurrence of Rh-negative blood type in three of the mothers. Large numbers of children with similar perinatal insults need to be looked at before developmental disabilities can be attributed to inherited factors rather than trauma or anoxia.

References
THE ETIOLOGY OF SO-CALLED SCHIZOPHRENIC PSYCHOSES

With Special Reference to Their Occurrence in Twins

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The main object of this communication is to report a study of 142 pairs of twins with so-called schizophrenic psychoses in one or both of the twins in each pair.

These twins are classified as follows: monozygotic 41 pairs; same-sex dizygotic 53 pairs; opposite-sex dizygotic 48 pairs.

There is a marked contrast between monozygotic and dizygotic twins with respect to the proportion of cases of both twins of the pair affected. These proportions are, respectively, 68.3 per cent and 14.9 per cent.

In the medical literature of twin pathology great stress has been laid on close similarity or even identicalness of manifestations, particularly in monozygotic twins. However, as regards the so-called schizophrenic psychoses, close similarity or identicalness of manifestations is the exception rather than the rule.

Instances of similar psychoses, quantitative dissimilarity (i.e., dissimilarity of age of onset, particular symptomatology, course, outcome, etc.), qualitative dissimilarity (i.e., one twin having a schizophrenic psychosis and the other some neuro-psychiatric condition belonging to a different clinical group, such as mental deficiency, epilepsy, etc.), and total discordance (i.e., one twin having a schizophrenic psychosis and the other not affected at all), are to be found among both monozygotic and dizygotic twins, but not with the same relative frequencies.

With reference to these points our material has been summarized in Table 3. The data thus revealed suggests the following general propositions:

1. In the etiology of so-called schizophrenic psychoses hereditary factors seem to play an important part.

2. The hereditary factors, in themselves, are often inadequate; that is to say, they do not suffice to produce a schizophrenic psychosis.

3. The pathogenic effect of the hereditary factors is not highly specific. Other factors often play a part with resulting dissimilarities of manifestation or total discordance of findings even in monozygotic twins.
4. Hereditary factors are not always present, therefore not essential, in the etiology of so-called schizophrenic psychoses.

A more detailed scrutiny of the material suggests the possibility of separating out, from amongst the so-called schizophrenic psychoses, a large group of cases which seem to occur on a basis of partial decerebration, mainly of traumatic or infectious origin.

The proportion of cases with a probable traumatic or infectious etiology seems to be higher in the male than in the female sex. The most prominent factor here seems to be cerebral birth trauma.

This is in harmony with other evidence, which we have published elsewhere, indicating a more marked cerebral vulnerability in male than in female fetuses and infants.

On the other hand, psychic factors in the etiology of so-called schizophrenic psychoses, especially in the sphere of sex or love life, seem to be more commonly found in women than in men.

As further evidence of the existence of at least two practically unrelated groups of psychoses among the so-called schizophrenias, attention is called to state hospital statistics pertaining to "dementia praecox." The two groups are unevenly distributed as to age and sex. While on the whole "dementia praecox" is somewhat more prevalent in the male sex, it is much more common in males than in females in the age group under 35, and is much more common in females than in males in the age group over 35.

In the group of cases which occur more characteristically in women and in later adult life and in which psychogenic factors appear more prominently in the etiology, hereditary factors seem to play a more important part than they do in the group characterized by a traumatic or infectious etiology.

In connection with psychotic disease resulting from intra-natal or post-natal trauma, the point must be specially stressed of its possible occurrence as a sequel following a seemingly insignificant trauma after an interval of 20 or more years.

We submit, as a part of our theory of so-called schizophrenic psychoses, that a large proportion of such psychoses originate in a cerebral trauma at birth or in childhood; that such cases are more prevalent in the male than in the female sex, and in young subjects than in those over 30 years of age; that the type of injury is often asymptomatic, or almost so, at the time of its occurrence; that it probably consists in subarachnoid and subpial hemorrhages upon the cerebral convexity in the frontal and parietal regions; and that it results in partial avulsion or detachment of the pia-arachnoid from the top and side surfaces of the gyri, causing interference with the blood supply, slow atrophy, and progressive impairment of mental function.

Further research is needed in this field. A series of 12 criteria is postulated as being demanded by our theory for the establishment of any given syndrome as a decerebration syndrome which may result from birth trauma.
An attempt to apply these criteria to the so-called schizophrenic psychoses reveals that for a roughly separable group of such psychoses 7 of the 12 criteria definitely fit.

Concerning the remaining five criteria nothing definite can be said either one way or the other on the basis of data which are readily available at this time. Certainly not one of them can be shown to not fit.

There is need for further research also in order to clarify the nature, mental mechanisms, symptomatology, and course of so-called schizophrenic psychoses which developed more characteristically in the thirties or later and more often in women than in men. Should it prove possible to isolate in a more clear-cut way this group of cases, opportunities would thereby be created for more definitely directed and more purposeful research along these lines too.