History of Autism

- **Term** *autism* originally used by Bleuler (1911)
  - To describe withdrawal from social relations into a rich fantasy life seen in individuals with schizophrenia
  - Derived from the Greek *autos* (self) and *ismos* (condition)

- **Leo Kanner – 1943**
  - Observed 11 children
  - Inattention to outside world: “extreme autistic aloneness”
  - Similar patterns of behavior in 3 main areas:
    1. Abnormal language development and use
    2. Social skills deficits and excesses
    3. Insistence on sameness
History of Autism

- Psychiatrist Hans Asperger (1944) - describes “little professor” syndrome
- Eisenberg and Kanner (1956)
  - Added autism onset prior to age 2
  - Further refined definition of autism
- Creak (1961)
  - Developed 9 main characteristics
  - Believed they described childhood schizophrenia
  - Incorporated into many descriptions of autism and commonly used autism assessment instruments today
History of Autism

- Rutter (1968)
  - Said the term *autism* led to confusion!
  - Argued autism was different than schizophrenia
    - Higher M:F ratio
    - Absence of delusions & hallucinations
    - Stable course (not relapse/marked improvement)
  - Further defined characteristics (for science, research)
- National Society for Autistic Children
  - One of the 1st & most influential parent groups for children with autism in U.S.
  - Wrote separate criteria (for public awareness, funding)
    - Added disturbances in response to sensory stimuli & atypical development
    - Did not include insistence on sameness
DSM Category: PDDs

Pervasive Developmental Disorders

- Autistic Disorder
- Rett’s Disorder
- Asperger’s Disorder
- Childhood Disintegrative Disorder
- PDD-Not Otherwise Specified
Autism

Communication & language deficit

Repetitive & stereotyped behaviors

Social interaction deficits

Seizures

Sensory sensitivity

Self-injurious behavior

Sleep disturbance

Mental retardation

GI problems

Immune problems
Assessment & Diagnosis

The NICHD lists these five behaviours that signal further evaluation is warranted:

– Does not babble or coo by 12 months.
– Does not gesture (point, wave, grasp) by 12 months.
– Does not say single words by 16 months.
– Does not say two-word phrases on his or her own by 24 months.
– Has any loss of any language or social skill at any age.
Assessment & Diagnosis

• It’s easier to ‘spot’ autism at the low functioning end of the spectrum.
• High functioning children do adapt.
• Early intervention is critical.
  – Younger children have a greater degree of brain plasticity (Edelman, 1992).
• Late screening:
  – Very few tools sensitive to adolescent/adult diagnosis.
  – Self-diagnosis common (AQ published on web).
Chart is updated from Autism Speaks: adds CDC 2012
Increase in Autism Appears Specific

Figure 3: Cumulative Percentage Change of Autism, Cerebral Palsy, Epilepsy, and Mental Retardation over Two Decades
Explanations for the rise in autism

- **Increase in diagnosis, not actual incidence**: better ascertainment; financial and scholastic support is linked to this diagnosis; changing or broadening of criteria of diagnosis
- **Increase in maternal auto-immune disease and obesity**: These disorders are increasing and are associated with increased risk for ASD in the offspring
- **Hygiene hypothesis**: cleaner environment leads to deficiency in educating the immune system as well as *increased asthma, allergies and autoimmune disorders*; over-use of antibiotics and anti-fever medications may also contribute
- **Environmental toxins**:
  - Lead
  - PCBs (polychlorinated bi-phenyls)
  - Organophosphate pesticides
  - Endocrine disruptors
  - Automotive exhaust
  - Polycyclic aromatic hydrocarbons
  - Brominated flame retardants
  - Perfluorinated compounds
“Trendy” Theories of Autism.

• Vaccines, MMR.
• Allergies.
• Gut/Intestine problems.
• Food intolerance.
• Environmental toxins.
• Refrigerator Mothers.
• Poor Parenting.
• Vitamin Deficiency.
Etiology: Vaccines

- **Vaccines**
  - Thimerosal - Preservative used in MMR vaccine used to contain mercury
  - Wakefield et al. (1998)
    - 12 children with PDD and gastrointestinal disease
    - Purpose was to look at relationship between these
    - Participants were selected because they had been referred to a pediatric gastroenterology dept for tx of intestinal problems (e.g., diarrhea, pain, bloating)
    - Onset appeared to be near time of MMR vaccination
    - Theory...MMR led to impaired intestinal functioning
      - Permeability of the intestines increased
      - Resulted in excess absorption of peptides from food
      - The peptides have opioid effects
      - Opioid excess led to brain dysfunction, and...
      - Concluded that ASD was caused by MMR vaccine
Etiology: Vaccines

• **Wakefield Study**
• **Methodological Issues**
  – Didn’t discuss specific diagnoses of participants (or how obtained)
  – The exact onset of intestinal problems wasn’t known
  – Evidence for link b/w behavior changes and MMR was based on report
  – Correlational study only
The graph shows the relationship between sales and the number of individuals diagnosed with autism and organic food sales over the years from 1997 to 2009. The correlation coefficient is r = 0.9971 (p < 0.0001), indicating a strong positive correlation between the two variables.

Sources: Organic Trade Association, 2011 Organic Industry Survey; U.S. Department of Education, Office of Special...
Etiology: Vaccines

• **Wakefield Study**
• **Methodological Issues**
  – Didn’t discuss specific diagnoses of participants (or how obtained)
  – The exact onset of intestinal problems wasn’t known
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  – Correlational study only
• **Ethical Problems**
• **Financial and scientific conflicts** that Dr. Wakefield did not reveal in his paper.
• **For instance**, part of the costs of Dr. Wakefield’s research were paid by lawyers for parents seeking to sue vaccine makers for damages.
• **Dr. Wakefield was also found to have patented in 1997 a measles vaccine** that would succeed if the combined vaccine were withdrawn or discredited.
Etiology: Vaccines

• In 2004, 10 of the 13 authors on the Wakefield et al. study published an article in the same journal (*The Lancet*) retracting the conclusions made in the original article.

• In 2010, the Lancet retracted the study altogether.

• In May, 2010, Wakefield was banned from practicing medicine in Great Britain due to unprofessional conduct.
Etiology: Psychodynamic Theory

- Eveloff (1960) – parents are cold, detached, ritualistic
- Bruno Bettelheim (1967)
  - Coined term “refrigerator mothers”
- No empirical support
Aetiology And Theories Of Autism.

- Genetic/biological factors.
  - 2-4% rates for siblings.
  - MZ twins up to 96% concordance.
  - DZ twins up to 27% concordance.
  - More common after chromosomal, infections, traumatic insults to CNS.

- One of the hallmarks of Autism is that the characteristics vary significantly among different children with autism. No two children with Autism are the same.
Etiology: Genetic Evidence

- Strong evidence for genetic component, but nature of the component is unknown
- Monozygotic twin concordance high, but less than 100%
Gene: a basic physical and functional unit of heredity that is transferred from a parent to offspring and is held to determine some characteristic of the offspring.
a distinct sequence of nucleotides forming part of a chromosome, the order of which determines the order of monomers in a polypeptide or nucleic acid molecule which a cell (or virus) may synthesize
### The genetic code

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**Note:** The table represents the standard genetic code, where codons are composed of three nucleotides (1st, 2nd, and 3rd letter). Each codon specifies a particular amino acid (e.g., Phe, Ser, Leu). The codons UAG, UGA, and UAA are stop codons, indicating the end of a protein sequence.
Left:
Green Fluorescence Protein (GFP) 3D Structure

Right:
Jellyfish Aequorea victoria. GFP from this organism
Rough estimates suggest that about 1 nucleotide in every $10^{10}$ is altered and inherited by daughter cells.
Possible genetic mutations

Wild type

mRNA 5' A U G A A G U U U G C U A A 3'

Protein Met Lys Phe Gly Stop

Amino end Carboxyl end

Base-pair substitution

No effect on amino acid sequence

U instead of C

AUGAAAGUUGCUAA

Met Lys Phe Gly Stop

Missense

A instead of G

AUGAAAGUUUGCUAA

Met Lys Phe Ser Stop

Nonsense

U instead of A

AUGUAGUUGCUAA

Met Stop
Possible genetic mutations

Wild type

mRNA 5' Protein
Amino end

3' Carboxyl end

1. Base-pair insertion or deletion
   - Frameshift causing immediate nonsense
     - Extra U
     - AUGUAAGUUUGGCUA
     - Met
     - Stop

   - Frameshift causing extensive missense
     - U Missing
     - AUGAAGUUUGGCUA
     - Met Lys Leu Ala ...

   - Insertion or deletion of 3 nucleotides:
     - no frameshift but extra or missing amino acid
     - AAG Missing
     - AUGUUUGGCUA
     - Met Phe Gly Stop
Genetics of human disease

Autosomal dominant pedigree

KEY

- Affected Male
- Affected Female
- Wild Type Male
- Wild Type Female
Autosomal recessive pedigree
De novo mutations
No family history of hereditary cancer

Mutation occurs in egg or sperm cell before fertilization, or immediately after fertilization.

Affected offspring

Diagrammatic representation of De Novo mutation (Adapted from the National Cancer Institute and the American Society of Clinical Oncology)
The progress of sequencing technology

Sanger sequencing (1977-present)
1) Collect blood
2) Extract and fragment DNA
3) Capture exome DNA with probes
4) Recover only exome DNA fragments
5) Sequence on next-generation platform