Biomedical update:

Asperger's, autism: family link?

G. Robert DeLong and Judith Dwyer report that Asperger's syndrome occurs frequently in family members of high-functioning autistic people.

Asperger's syndrome (see ARRI Vol. 2, No. 4) is considered by some researchers to be a separate disorder from autism. People diagnosed as having Asperger's syndrome usually have normal or above-normal IQs, live independently, and desire social relationships; however, they are socially inept, have fixations and peculiar language patterns, and tend to be uncoordinated.

DeLong and Dwyer found that while many high-functioning autistic people had a family history of Asperger's syndrome, low-functioning autistic people did not. "In contrast," they say, "low-functioning autistics have a high incidence of abnormal neurological findings on EEG or CT scan, whereas high-functioning individuals have a much lower incidence."

In addition, the researchers found that manic depression is more common in families of autistic people (both high- and low-functioning) than in the general population. The incidence of manic depression was higher in families of higher-functioning autistic children, and highest in the families with a history of Asperger's syndrome. While the incidence of manic depression was elevated, the incidence of unipolar affective disorder (depression alone) was not.

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"Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disease," G. Robert DeLong and Judith T. Dwyer; *Journal of Autism and Developmental Disorders*, Vol. 18, No. 4, December 1988, pp. 593-600. Address: G. Robert DeLong, Division of Pediatric Neurology, Duke University Medical Center, Durham, North Carolina 27710.

Fenfluramine toxicity?

In previous issues of ARRI we have reviewed the many conflicting studies on the value of the drug fenfluramine (Pondimin) in treating autistic children (see ARRI Vol. 1, No. 3). The review article, as well as a subsequent short article (ARRI Vol. 2, No. 4) addressed the question of possible toxicity of fenfluramine to brain cells.

The January 6, 1989 issue of the journal *Science* has added new fuel to the neurotoxicity controversy. A study by researchers Stephen Peroutka and John Warner was described in which fenfluramine was found to be three times more toxic to rats than the street drug Ecstasy (MDMA). Single high doses of fenfluramine caused a 50% depletion of the sites on nerve cell membranes that recycle the brain transmitter serotonin back into the cells. In addition, Errol De Souza and colleagues report that high doses of fenfluramine may cause physical damage to serotonin nerve terminals.

Other researchers, cited in both the original *Science* article and in a February 24, 1989 letter to *Science* from the manufacturers of fenfluramine, argue that there is no conclusive proof that fenfluramine is neurotoxic in humans. Rat studies, they point out, have questionable relevance to humans. (Rat studies do have the advantage that one can dissect the rat brain to look for damage.)

A recent British double-blind placebo cross-over study of the effects of fenfluramine on 20 autistic subjects found no significant differences between fenfluramine and a placebo. Based on their findings, the researchers say they "would not advocate its [fenfluramine's] widespread use in autistic patients." An open clinical trial in France, on the other hand, indicated that fenfluramine reduced hyperactive behavior in 75% of 44 autistic children tested.

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"Neurotoxicity creates regulatory dilemma," Deborah M. Barnes; *Science*, January 6, 1989; letter, *Science*, February 24, 1989.

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"Effects of fenfluramine on autistic symptoms," J. A. Kohler, G. Shortland, and C. J. Rolles; *British Medical Journal*, October 10, 1987, 295, 885. Address: J. A. Kohler, Department of Paediatrics, Southhampton Gen. Hospital, Southampton SO9 4XY England.

—and—

"Evaluation du traitement par la fenfluramine dans l'autisme infantile," R. De Villard, B. Ceillier-Hoppenot, E. Flachaire, J. Dalery, B. Rebaud, J. Maillet, O. Revol, J.C. Mamelle and C. Quincy; *Pediatrie*, 43, 1988, pp. 703-708. Address: R. De Villard, Hopital neurologique, 59, bd Pinel, 69003 Lyon et Hopital psychiatrique du Vinatier, 95, bd Pinel, 69500 Bron, France.

Autopsy reveals defects

A third autopsy study by Margaret Bauman and Thomas Kemper has revealed the same defects in the limbic system and cerebellum reported in two previous studies (see ARRI Vol. 1, No. 1).

Abnormal areas of the limbic system included the hippocampal complex, entorhinal cortex, and amygdala. The anterior cingulate gyrus, septal nuclei and mammillary body also were involved. In the cerebellum, there was a loss of Purkinje cells and granule cells, with a preservation of neurons in the inferior olive.

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"Limbic and cerebellar abnormalities—consistent findings in infantile autism," Margaret Bauman and Thomas Kemper; *Journal of Neuropathology and Experimental Neurology*, Vol. 47, May 1988, page 369. Address: either author at Neurological Unit, Medical Bldg., Rm. 913, Boston City Hospital, 818 Harrison Ave., Boston, MA 02118.

Retinoblastoma noted

Edward Ritvo and colleagues report that they have seen a 19-year-old autistic girl with retinoblastoma, a hereditary eye tumor. A distant relative (a maternal great uncle's grandson) also is autistic.

The researchers note that mental retardation has been reported in three to seven percent of people with retinoblastoma, and that most of these cases also involve a deletion on chromosome 13 and reduced activity of the enzyme esterase D—two symptoms also present in this case. The UCLA group previously reported a weak genetic linkage between autism and the chromosome area associated with Esterase D.

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"Association of autism, retinoblastoma, and reduced esterase D activity" (letter), Edward Ritvo, John Menkes and Robert Sparkes; *Archives of General Psychiatry*, Vol. 45, June 1988, page 600. Address: Edward Ritvo, Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024.

Males with Rett symptoms?

Some males have hand-washing stereotypies and other symptoms similar to those seen in Rett syndrome, according to Japanese researchers. Rett's has generally been believed to affect only girls.

The researchers found 16 males with hand-washing movements; nine had cerebral palsy, five were autistic, one had spinal muscular atrophy, and one was a child with Down syndrome. Eleven had epilepsy or related neurological disorders.

The hand-washing movements of the subjects were shorter in duration than is typical in Rett syndrome, but similar in manner. Other Rett-like symptoms in the male group included microcephaly (small head size) in eight cases and scoliosis (curvature of the spine) in four cases. Also reported in some cases were abnormal gait, loss of purposeful hand use, loss of speech or gesturing ability, and histories of normal development followed by regression.

Editor's Note: Dr. Michel Philapart of UCLA informs ARRI that he has seen two males who are arguably Rett cases. The newest criteria for Rett's do not exclude males, though the question is being debated.

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"Clinical analysis of male cases with hand-washing-like stereotypies similar to those in Rett syndrome," Tatsuo Takeuchi, Akiko Matsumoto, Toshiyuki Kumagai, Shuji Miyazaki, Hiroshi Ono, and Kazuyoshi Watanabe; *Brain and Development*, Vol. 9, No. 2, 1987, p. 217. Address: Tatsuo Takeuchi, Dept. of Ped. Neur., Central Hospital, Aichi Prefectural Colony, Kasugai, Aichi, Japan.