Biomedical Update:

Animal study links metal exposure to hypersensitivity

The evidence linking heavy metal exposure to the immune system abnormalities in autism became stronger recently, with the publication of an animal study linking metal toxicity to immune dysregulation.

Antje Kakuschke and colleagues collected blood samples from harbor seals, and measured concentrations of 20 essential and non-essential elements. The researchers report that high metal concentrations correlated significantly with metal-specific hypersensitivities, with 7 of 11 tested seals showing such hypersensitivities. "Four animals responded to one metal," they note, "and three animals to multiple metals." Sensitizing metals included molybdenum, titanium, nickel, chromium, aluminum, lead, and tin. Unpublished data from the research group reveals that the lymphocytes of newborn seals are especially vulnerable to the immunotoxic effects of metals.

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"Immunological impact of metals in harbor seals (Phoca vitulina) of the North Sea," Antje Kakuschke, Elizabeth Valentine-Thon, Simone Griesel, Sonja Fonfara, Ursula Siebert, and Andreas Prange, *Environmental Science and Technology*, August 17, 2005 (web publication). Address: Antje Kakuschke, Institute for Coastal Research, GKSS Research Centre, aMax-Planck-Strasse 1, 1 21502 Geesthacht, Germany.

Cylert loses FDA approval due to toxicity

Cylert (pemoline), a drug prescribed for attention deficit hyperactivity disorder, autism, and related disorders, has lost its FDA approval but will not be removed from the market. Instead, pharmacies will be allowed to sell remaining stockpiles of generic equivalents of the drug, which was discontinued by Abbott Laboratories earlier this year.

Evidence linking Cylert to severe liver problems, sometimes resulting in liver transplants or death, began surfacing in the 1970s. However, the FDA continued to approve the drug, while requiring in 1996 that the company add a "black box" warning—the strongest drug warning—about the potential for liver damage. The warning was strengthened in 1999. However, since that time, 21 additional cases of liver failure, including 13 cases involving deaths or liver transplants, have been reported to the FDA. Says the consumer group Public Citizen, which lobbied for a ban on the drug, "Because only 10 percent or so of adverse events are reported to the FDA, these are clearly underestimates of the true number of such cases." The drug is already banned in the United Kingdom and Canada.

Public Citizen is criticizing the FDA's decision not to ban the drug, saying, "It is reckless and insensitive to the health and lives of children and adults using this drug for the FDA and the involved drug companies to fail to institute an immediate recall of these dangerous products." The organization charges that there is no evidence to support claims that the drug is superior to other ADHD treatments.

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"FDA withdraws approval for ADD drug," Associated Press, October 24, 2005.

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Blood glucose levels affect problem behavior

Blood glucose levels can be a factor in developmentally disabled children's problem behavior, according to a recent case study. ***(Editor's note: This finding may be particularly relevant to autistic children taking newer atypical psychotropic drugs such as olanzapine and risperdal, which can cause dramatic elevations in blood glucose levels.)***

Maria Valdovinos and David Weyand analyzed the behavior of a profoundly retarded adolescent girl with Angelman syndrome and Type I diabetes. The girl's behavior problem included aggression, self-injury, throwing objects, and throwing herself to the floor.

The researchers report, "Generally, when blood glucose levels exceeded the [normal] range or were on the high end of the range, rate of problem behavior was higher than when the blood glucose levels were within or below range." Aggression occurred more often when the girl's blood glucose levels exceeded the normal range, while self-injury occurred less often in this condition. The researchers say the latter finding suggests that the girl became more sensitive to pain when her blood glucose levels were elevated. She was also less compliant to demands during high-blood-glucose periods.

Valdovinos and Weyand say that their single case study should be interpreted with caution, but recommend that future research evaluate the effects of differing blood glucose conditions on problem behavior in individuals with developmental disabilities.

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"Blood glucose levels and problem behavior," Maria G. Valdovinos and David Weyand, *Research in Developmental Disabilities*, July 6, 2005 (epub ahead of print publication). Address: Maria Valdovinos, maria.valdovinos@DRAKE.edu.

Clozaril a strong risk factor for diabetes

The newer "atypical" antipsychotic drugs appear to strongly increase the likelihood of developing diabetes, and a new study indicates that clozapine (Clozaril) poses an especially high risk.

J. Steven Lamberti and colleagues evaluated 101 individuals with schizophrenia or schizoaffective disorder receiving clozapine treatment through an outpatient clinic. The average age of the patients was 40.4 years. The researchers analyzed the patients' demographic data, body mass index (BMI), and body fat measurements, and used medical records and blood glucose testing to establish diagnoses of diabetes.

The prevalence of diabetes in the group was 25.7 percent, compared to a rate of 14.9 percent rate for adults in the general population. The average duration of clozapine treatment was 5.7 years, and patients who developed diabetes did so an average of 3.7 years after starting to take the drug. Nonwhite patients and those with a family history of diabetes were at greatest risk. Interestingly, there was no significant correlation between BMI or body fat and the risk for developing diabetes.

While atypical antipsychotics typically cause weight gain, which can increase the risk for diabetes, Lamberti says that "clozapine may cause diabetes by directly affecting pancreatic beta cells, glucose transport or other mechanisms independent of weight gain in certain susceptible individuals."

Lamberti and colleagues note that other risk factors, such as poor diet, lack of exercise, substance abuse, and schizophrenia itself could elevate the risk for diabetes in their patient group. They conclude, however, that "patients receiving clozapine are at substantial risk for developing diabetes, although the level of risk relative to other antipsychotic medications has not been fully determined." The researchers caution doctors prescribing clozapine to closely monitor patients—particularly patients with family histories of diabetes—very carefully for signs of diabetes.

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"Diabetes mellitus among outpatients receiving clozapine: prevalence and clinical-demographic correlates," J. S. Lamberti, G. O. Costea, D. Olson, J. F. Crilly, K. Maharaj, X. Tu, A. Groman, M. B. Dietz, M. P. Bushey, T. Olivares, and K. Wiener, *Journal of Clinical Psychiatry*, Vol.. 66, NO. 7, July 2005, 900-6. Address: J. S. Lamberti, Department of Psychiatry, University of Rochester Medical Center, Rochester, NY 14642, steve_lamberti@urmc.rochester.edu.