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Letters

The Letters *column is a forum for rapid exchange of ideas among readers of* Clinical Pharmacy. *Liberal criteria are applied in the review of submissions to encourage contributions to this column.*

The Letters *column includes the following types of contributions: (1) comments, addenda, and minor updates on previously published work, (2) alerts on potential problems related to drug therapy or clinical research, (3) observations or comments on trends in drug therapy or clinical research, and (4) brief expressions of opinion about controversies in drug therapy or clinical research.*

Letters need not be submitted with the journal's manuscript checklist. The following conditions, however, must be adhered to: (1) the body of the letter must be no longer than two typewritten pages, (2) the use of references, tables, and illustrations should be minimized, (3) the authors' names, affiliations, and mailing addresses must be typed at the end of the letter in the format used by Clinical Pharmacy, *and (4) the entire letter (including references, tables, and authors' names) must be typed double-spaced on plain white paper (not letterhead). Following acceptance of a letter, the authors are required to sign an exclusive publication statement and a copyright transferal form.*

Hyperthyroidism associated with mercury poisoning

The paper on elemental mercury poisoning recently published in *Clinical Pharmacy*[1] prompts us to report a personal experience that suggests a relationship between long-term mercury exposure and certain autoimmune disorders.[2,3]

One of us, a 52-year-old man (hereafter called the patient), had practiced general dentistry from 1964 to 1984 and had a toxic mercury exposure in 1978 after mercury was spilled onto carpeting in his work area. In addition, the patient had regularly removed mercury–silver (amalgam) dental fillings with a high-speed drill, and his amalgamator was found to leak mercury.

The patient gradually developed nausea, indigestion, weight loss, tachycardia, fatigue, tremor, anxiety, and panic attacks associated with feelings of impending death. Symptoms improved when he was away from his office for prolonged periods. Finally, symptoms of peripheral numbness, cold sweats, chills, tachycardia, and recent memory loss prompted a neurologic investigation, which revealed encephalopathy. By the time mercury toxicity was suspected, the patient was disabled and had to give up his practice.

During initial chelation therapy with edetate calcium disodium, the serum thyroxine (T_4) concentration rose from 8 to 27 μg/dL (normal, 4.5–12 μg/dL). Uptake of radioactive iodine by the thyroid gland was high. The patient was treated with propylthiouracil for hyperthyroidism. Current values of thyroid function tests are serum T_4 concentration, 7.8 μg/dL; serum thyroid-stimulating hormone concentration, 1.3 μU/mL (normal, 0.5–5.0 μU/mL); and triiodothyronine uptake, 33.1% (normal, 25–35%). The titer of antithyroglobulin antibody was elevated at 1:320 (normal, up to 1:10), and the value from a second (repeat) determination was 1:80; the titer is now normal. The titer of antimicrosomal thyroid antibody was 1:400 (normal, up to 1:100) and remains at the same value. The patient is clinically euthyroid and takes no medication.

It is unlikely that this spontaneous development of and recovery from hyperthyroidism was coincidental. Studies for the presence of the following autoantibodies were negative: antinuclear, anti-double-stranded DNA, anti-RNA, anti-soluble-nuclear antigen, anti-La (La is an extractable nuclear antigen formerly called SS A), anti-RO (RO is another extractable nuclear antigen, formerly SS B), antiadrenal, and antiscleroderma. These results suggest autoimmunity specific for thyroglobulin in this pa-

tient. The concentration of circulating immune complexes, measured by two nonspecific methods, was higher than normal. The numbers of T and B cells were normal. Mercury induces immune-complex formation in rats and mice.[3] The laboratory results above suggest that mercury may have been intimately, albeit indirectly, related to the symptoms and signs of hyperthyroidism in this patient.

There is evidence in animals that mercury alters the sulfur–hydrogen bond in various molecules, including hemoglobin, immunoglobulins, thyroxine, and even insulin.[4,5] In this regard, it is notable that the patient had transient polycythemia; the hematocrit was 54.5% and is now 50%. Mercury may also alter normal hemoglobin molecules, an effect that could signal the body's immune system to recognize the altered hemoglobin as nonself.

The total body burden of mercury in cases of toxicity in humans is difficult to measure clinically, but the half-life of mercury in the central nervous system in mammals is much longer than that in other tissues.[6,7] This may account for a continued abnormal antigen drive long after the mercury concentration in extracellular fluid becomes normal.

It is also possible that the varied clinical manifestation of mercury exposure—the fact that some persons become ill and others do not—is related to the individual's specific class II HLA histocompatibility antigens that control recognition of foreign antigens.

The effects of mercury exposure should be vigorously investigated using modern immunologic techniques. Although mercury's toxic potential is now recognized—in this country, mercury can no longer be an ingredient of interior paints, and Sweden will prohibit the use of mercury-containing dental amalgams starting in 1992—exposure to the element is still widespread. The mercury–silver dental fillings used in the United States, for example, contribute heavily to Americans' total body burden of mercury.[8] Because immunoglobulins are important in fetal organogenesis, and because the fetus is particularly sensitive to maternal mercury exposure,[9] it is particularly important to study the immunologic effects of mercury in pregnancy.

Mercury exposure should be considered for more than its classic toxicological effects. Even minuscule amounts of a foreign antigen or hapten, such as mercury, can have profound clinical effects in genetically susceptible individuals. The link between autoimmune disorders, such as thyroid dysfunction, and mercury should prove to be an important and fertile topic of investigation.[2,3,10-12]

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MICHAEL MCCANN, M.D.
Department of Allergy and Immunology
Kaiser Medical Center
12301 Snow Road
Parma, OH 44130

STUART SCHECKNER, D.D.S.
4854 Primrose Path
Sarasota, FL 34242

Ethnicity and clozapine-induced agranulocytosis

Bond[1] suggested in the June issue of *Clinical Pharmacy* that "the influence of ethnicity on psychotropic drug disposition and effect will become increasingly important in clinical practice." Ethnicity may also play a role in the development and severity of psychotropic-induced adverse effects, as has been reported with the new antipsychotic agent clozapine.[2-4]

The major adverse effect of clozapine is agranulocytosis, and this reaction was noted to be especially dangerous and prevalent during an "epidemic" in southwest Finland in 1975.[3-5] The frequency of agranulocytosis during this outbreak was approximately 21 times greater than that observed in other countries.[3,4] Local genetic or environmental factors may have been involved in the Finnish cases, but they have yet to be elucidated.[3,4]

More recently, it has been found that a disproportionate number of clozapine-treated patients in the United States who have developed agranulocytosis during treatment have been of eastern European Jewish heritage.[2] Results of genetic typing have indicated that a genetic factor may be associated with the susceptibility of Jewish patients to develop agranulocytosis when treated with clozapine.[2] In addition, the frequency of some phenotypes common among the Ashkenazi Jewish population is greatly increased in patients who develop clozapine-induced agranulocytosis.[2]

No studies comparing the pharmacokinetics of clozapine in different ethnic groups have been performed. In addition, there are no recommendations about dosage or about precautions, such as intensified hematologic monitoring, for Finnish or Jewish patients treated with clozapine. Nevertheless, the possible genetic factors involved in the development of agranulocytosis should be consid-

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