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Attention Deficit Hyperactivity Disorder and Blood Lead Levels in Chinese Children

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In their study of the relationship of blood lead levels (BLLs) in children 4–12 years of age and attention deficit hyperactivity disorder (ADHD), Wang et al. (2008) considered potential confounding variables and covariates with considerable thoroughness. For certain of these (e.g., low birth weight), the proportion of affected children generally accords well with reported prevalence in other settings [UNICEF and World Health Organization (WHO) 2004]. However, this was not so with case children with a family history of ADHD described by Wang et al. (2008). Only 21 (3.3%) of the 630 cases in their study had such a history.

ADHD and other externalizing disorders (e.g., conduct disorder) are known to have substantial genetic components, and ADHD heritability has been estimated to be 75% (Biederman and Faraone 2005; Gelhorn et al. 2006). Among children with ADHD or earlier definitions of the disorder, the reported proportions with at least one affected parent or sibling range from 9% to 64% (Biederman 2005; Biederman et al. 1990, 2008; Milberger et al. 1998; Roizen et al. 1996; Schachar and Wachsmuth 1990). This substantial body of work suggests a figure of 20–25% as a reasonable estimate of the proportion of first-degree relatives afflicted with ADHD, or 6–8 times that reported by Wang et al. (2008) in the families of their case children.

Wang et al. (2008) assessed family history of ADHD by psychiatric diagnoses noted in clinical reports. It is possible that such information was not systematically acquired in previous years and is thus underrepresented in these reports. This would actually be likely if ADHD was less well-defined or considered less often as a diagnosis in Anhui Province, China, when the parents of the 4- to 12-year-old children included in this study were of similar age. It is also possible that ADHD in this setting differed in some way from ADHD in other settings, although the rigorous diagnostic criteria used by the authors make this explanation less plausible.

In their backward stepwise logistic model (their Table 3), Wang et al. (2008) showed that ADHD in the child is positively associated with family history of ADHD and BLL ($\geq 10 \mu\text{g/dL}$ vs. $\leq 5 \mu\text{g/dL}$ and 5–10 $\mu\text{g/dL}$ vs. $\leq 5 \mu\text{g/dL}$) and inversely associated with maternal education. Assuming that the

reported odds ratio of 5.65 for family history of ADHD remained unaltered, a 6- to 8-fold increase in the number of case children with this exposure would commensurately increase the relevant Wald statistic and almost certainly reduce the Wald statistics of the associations with BLL and/or maternal education, conceivably to nonsignificant levels.

Wang et al. (2008) stated that their results reinforce findings from two previous studies of the relationship of BLL to ADHD, but it is unclear how this is so (Braun et al. 2006; Nigg et al. 2008). In the study by Braun et al. (2006), the cut-point of the highest BLL exposure quintile, the only one associated positively and significantly with ADHD, was 2 $\mu\text{g/dL}$; in the study by Nigg et al. (2008), the mean BLL for the ADHD-combined group was 1.26 $\mu\text{g/dL}$. Yet the mean BLL in control children studied by Wang et al.—by definition, ADHD-free—was 5.76 $\mu\text{g/dL}$, nearly 3 times the level reported by Braun et al. and 5 times that of Nigg et al. In neither of the earlier studies did the researchers adjust the BLL–ADHD relationship for family history of ADHD.

Familial transmission of ADHD and its diagnostic forebears has been documented for more than three decades (Cantwell 1972), and systematic assessment of the contribution of familial inheritance has been under way for more than two decades (Biederman 1986). Studying risk factors for ADHD with incomplete or no control of family history of ADHD is like studying risk factors for lung cancer with inadequate control of smoking history (Stevens and Moolgavkar 1984). Doing so may answer some questions, but the main question remains unanswered.

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Jack Brondum

Environmental Health and Epidemiology
Hennepin County Department of Human
Services and Public Health
Hopkins, Minnesota

E-mail: jack.brondum@co.hennepin.mn.us

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Cancer Risk and *GSTM1* and *GSTT1* Polymorphisms

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Rossi et al. (2009) stated in their conclusion that “*GSTM1* [glutathione S-transferase M1] and *GSTT1* [glutathione S-transferase theta 1] polymorphisms [as all individual polymorphisms] ... are not expected to have a dramatic influence on baseline CA [chromosomal aberration] or overall cancer risk.”

We agree with these statements from a general point of view. However, it is one thing to suggest that an evident pathologic marker, such as CA frequency in peripheral lymphocytes, could be an expression of cancer (like elevated carcinoembryonic antigen or other biomarkers) and another to exclude any influence of a genetic polymorphism on the occurrence of a specific type of cancer on the basis of a study that is basically not suitable to answer the question.

We will not address the advantages of the Bayesian approach versus the classic frequentist model. However, as clinicians, we would like to comment on epidemiologic studies on cancer, in particular those concerning the possible effects of complex causative factors such as environmental pollution. We also will discuss issues concerning patients and outcomes of the article by Rossi et al. (2009). In particular, we will focus on issues that are often considered by epidemiologists and those interested in statistical analysis to be pathophysiologic or pathogenetic details, but are, on the contrary, basic issues for those examining clinical and pathological findings.

Although the combination of bone and skin cancers (cancers that originate from different tissues and are related to completely different pathogenetic agents and pathophysiologic mechanisms) could be acceptable from a statistical point of view, this practice creates a methodologic bias from pathophysiologic and pathogenetic points of view. Because Rossi et al. (2009) included a large number of bone and skin cancer cases in their study ($n = 20$ in their Table 2), it is of paramount importance to state whether cytochrome P451 A1 (CYP1A1) is a basic factor in the occurrence of these cancers. For lung and respiratory tract cancer, the role of CYP1A1 has been tested; however, it is not appropriate to use these polymorphisms, which are specific for the metabolism of some xenobiotics, as a marker of all cancers.

Our team has long been involved in the detection of cause and effect relationships between presumed causative factors and cancer, in particular, concerning the relative role of inherited predisposition and environmental factors, the relative impact of intrinsic toxicity or carcinogenicity, and the role of host susceptibility and response (Cetta et al. 2007, 2009a).

In a genome-wide analysis of copy numbers in couples in which either husbands had been occupationally exposed to asbestos but did not have mesothelioma or spouses with mesothelioma who had not been occupationally exposed to asbestos, we reported a panel of differently expressed genes that could be responsible for a different inherited susceptibility. This panel of differently expressed genes sometimes included genes involved in the control of major histocompatibility systems, in the production of drug-metabolizing enzymes, or of X-ray repair or mismatch repair genes (Cetta F, Dhama A, Zangari R, unpublished data).

Therefore, it is plausible that genetic polymorphisms in *GSTM1* and *GSTT1* may be part (if not the main determinant) of a panel of genes that define the individual susceptibility of some subjects to interact differently with a given environmental agent; this

interaction would lead to cancer as a final outcome only in the susceptible individuals and not in others, even if the nonsusceptible individuals are more exposed to the same toxic or carcinogenic agent.

We suggest that the pathogenetic task (i.e., a better knowledge of the variable impact of the same toxic agent on different individuals) requires very specific and focused studies and not generic studies that combine skin and bone cancer grouped by the same code.

We suggest that studies rely less on the statistical power of numbers (cases and controls) and pay more attention to the homogeneity of populations, groups, or subgroups. These studies should focus not only on the biological but also on the pathophysiologic and pathogenetic plausibility of observed data; they should avoid mixing “apples and oranges.”

We suggest that researchers examine data carefully before they state that one event is influenced or not influenced by a causative or facilitating agent, namely when interactions between cause and effect are very complex and the causative relationship is not clear-cut (Cetta et al. 2007, 2009b). This is even more important when attempting to establish the relative impact of inherited or environmental factors in the occurrence of various types of cancers, each of which has its own peculiarity and wide variations, even within the range of tumors affecting the same organ or tissue (Cetta et al. 2007, 2009a).

In the future, there will be a major need for improved knowledge of causative and pathophysiologic mechanisms and for more strict adherence to this knowledge before designing epidemiologic or pathogenetic studies. These studies must rely more on the homogeneity of the enrolled population and on the direct cause and effect relationship between the causative agent and the expected outcome, and less on the number of enrolled subjects (if subjects are not appropriate for the scope of the study, their inclusion is potentially misleading. Panel studies in smaller but well-selected groups will give more useful information than large population studies that are missing the pathophysiologic and causative targets, in particular when large studies are based on too many inferences and/or extrapolations from old or inhomogeneous data.

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Francesco Cetta*
Armand Dhama
Laura Moltoni
Rosalia Zangari

Department of Surgery
Research Doctorate in Oncology and Genetics

University of Siena
Siena, Italy
*PAT Geriatric Institute, Milan, Italy
E-mail: cetta@unisi.it

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Cancer Risk and *GSTM1* and *GSTT1* Polymorphisms: Hansteen et al. Respond

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We thank Cetta et al. for the interesting comments regarding our article (Rossi et al. 2009). In their letter they address two main issues. The first refers to the role of genetic polymorphisms in the causal relationships between exposure to carcinogens and cancer occurrence. The second is more conceptual and criticizes the evolution of association studies, claiming a decreased attention to pathogenetic mechanisms in favor of an indiscriminate increase of the study size, with a consequent lack of biological plausibility.

We agree that these are important issues. We have addressed the problem of inherited predisposition for DNA damage from a different angle, namely using the frequency of chromosomal aberration (CA) as a response indicator for occupational and environmental exposure to genotoxic agents. An increase in CA level in exposed individuals compared with controls has been documented since the 1990s (Nordic Study Group 1990). The conceptual basis for using this assay has been the hypothesis that the extent of genetic damage in peripheral lymphocytes reflects critical events for the carcinogenic process in target tissues.

The key issue—whether the association with cancer risk is attributable to exposure to carcinogenic agents or reflects inherited susceptibility and accumulated damages—was addressed with a nested case–control study on incident and deceased cancer cases in the Nordic and Italian cohorts (Bonassi et al. 2000). The main findings of that study indicated an increase in cancer risk for subjects with high CA levels compared with those with low levels. This increase was independent

of exposure history, as further verified in follow-up studies (Bonassi et al. 2008; Hagmar et al. 2004).

In all these studies, cancer has been studied as one entity. This summarization was mostly due to statistical needs, although the very early occurrence of chromosome damage in the carcinogenic pathway of most solid cancers provided a valuable rationale (Mitelman et al. 2004). A further reason for summarizing data by cancer type was that damages were measured in surrogate tissues and not in the target, providing only an indirect measure of cancer-related events. However, studying the cancer site in relation to CA frequency was a major interest of our group, because different types of cancers have different pathogenetic models. In our recent article (Rossi et al. 2009), we grouped cancer types into three groups, and we showed for all of these groups that subjects with high levels of CAs are more susceptible to developing cancer than are subjects with low or medium levels of CAs; this indicates that CA is an inherited susceptibility marker for cancer regardless of cancer type.

The beginning of Cetta et al.'s letter is misleading. The statement from our article (Rossi et al. 2009) that "*GSTM1* [glutathione S-transferase M1] and *GSTT1* [glutathione S-transferase theta 1] polymorphisms [as all individual polymorphisms] . . . are not expected to have a dramatic influence on baseline CA [chromosomal aberration] or overall cancer risk" is not a conclusion of the study, but describes the conclusions of the extensive literature supporting this evidence (Hirschhorn 2009). We agree that it is important to examine the cause of different types of cancer and the role(s) of the different modifying enzymes, including *GSTM1* and *GSTT1*. However, the present study was designed to evaluate a possible modifying effect of *GSTM1* and *GSTT1* on the cancer predictivity of CA (indicating individual susceptibility to developing cancer). Our main concern was identify individuals more susceptible to damage from known genotoxic exposure. Because only *GSTM1* and *GSTT1* polymorphisms have been extensively evaluated in human surveillance studies, we tested only these genotypes. Within the consortium of studies included in this project (Bonassi et al. 2008), further follow-up studies to differentiate cancer types or include other genotypes are possible, providing adequate financial support.

The issue raised by Cetta et al. of decreased attention to pathogenetic mechanisms in favor of larger studies, with a consequent lack of biological plausibility, is only partially correct. Actually, in association studies that link a genetic polymorphism to the effect of exposure or to the risk of cancer, the

lack of specificity is the main reason for failure. Another reason for their failure is small study size, which generates meaningless and often contrasting results. The conflict noted by Cetta et al. is apparent because, as demonstrated by the success of genome-wide association studies, the need of reaching a proper statistical power is as important as studying a genetic polymorphism in a specific pathway.

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Inger-Lise Hansteen

Department of Laboratory Medicine
Section of Medical Genetics
Telemark Hospital
Skien, Norway

Anna Maria Rossi

Roberto Barale
Department of Biology
Pisa University
Pisa, Italy

Lisbeth E. Knudsen

Environmental Health
Institute of Public Health
University of Copenhagen
Copenhagen, Denmark

Hannu Norppa

New Technologies and Risks
Work Environment Development
Finnish Institute of Occupational Health
Helsinki, Finland

Stefano Bonassi

Unit of Molecular Epidemiology
National Cancer Research Institute
Genoa, Italy
E-mail: stefano.bonassi@istge.it

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Modern Environmental Health Hazards in Africa: Additional Comments

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I commend *Environment Health Perspectives* for publishing the work of Nweke and Sanders (2009); this significant contribution brought to light interesting aspects of environmental health hazards on the African continent that can be universalized for scientifically unrepresented less developed countries and regions of the planet. In this dimension, existing studies [World Health Organization (WHO) 1989] of that continent compel us to share additional results of studies of heavy metals (mercury, lead, and cadmium) related to early exposure in children. I would like to address the WHO (1989) study of breast milk concentrations used to monitor mother–infant contamination in selected African countries (Nigeria and Zaire). I would also like to point out an often neglected but universal source of Hg exposure during pregnancy and throughout infancy and childhood—ethylmercury (etHg) in thimerosal-containing vaccines (TCVs).

Concentrations of Hg and Pb in breast milk are important indicators of prenatal exposure, the period when most neurotoxic insults of these elements occur. In a review in which I summarized the WHO (1989) study, I showed that mean Hg concentrations were similar in both Nigeria and Zaire (Dórea 2004), but these concentrations were among the highest reported in that review (Dórea 2004). However, the concentrations of milk Pb were higher than that of milk Hg for both countries; in the case of Pb, mean Pb concentrations in rural Zairians were twice that of urban dwellers. On a molar basis, there was twice as much Pb as Hg in these African countries (Dórea 2004); however, the ratios of Se and Ca concentrations (attenuators of neurotoxicity of Hg and Pb) were quite different between the two countries.

Nweke and Sanders (2009) realized that the earliest stages of neurodevelopment are most vulnerable to the toxic effects of Hg. Therefore, I find the figures of occupational exposure involving mothers to be disturbing; women occupationally exposed to gold processing from amalgam range from 5% of the population in South Africa to 50% in Mali. Also, African women are exposed to Hg in soap and through traditional fish consumption. However, Nweke and Sanders (2009) did not mention that tetanus vaccines are used in countries following WHO recommendations to control or eradicate maternal and neonatal tetanus. These vaccines are preserved with thimerosal. In any part of the developing world where TCVs are in widespread use, a newborn is exposed

to high concentrations of *etHg* depending on the child's weight and vaccine brand (Dórea and Marques 2008). Indeed, because the hepatitis-B vaccine is given within hours of birth, Hg concentrations can reach extremely high levels of acute exposure, depending on birth weight and vaccine manufacturer (Dórea and Marques 2008). These exposures are higher than the ones estimated for occupationally exposed mothers working with gold extraction (Dórea 2009). Nweke and Sanders (2009) covered environmental hazards as a result of exposure to hazardous pollutants in tandem with development activities, as well as evidence of their adverse effects on African populations. However, they did not mention this important source of Hg exposure to which the fetus (during pregnancy), infant, or child is exposed.

Some African populations, due to lack of sanitation and hygiene, are more prone to preventable diseases and are, as a result, a target for vaccination campaigns for children's diseases; additionally, emergency measures may introduce specific vaccines for diseases that are rare (or nonexistent), eradicated, or controlled in other countries. Some of these vaccines, for operational reasons, need thimerosal as a preservative. Currently, because of the low cost, TCVs are routinely used in underdeveloped countries, whereas the

European Union, the United States, and other industrialized countries have stopped using them based on the plausibility that TCVs may affect neurodevelopment of young children. These precautionary measures need to reach the great majority of infants and young children around the world (including Africa).

Given the heterogeneous socioeconomic situation of African countries, differences in need for vaccines and the affordability of mass immunization programs are complex and difficult to study. Although I support mass vaccination, it is important to take into account characteristics of the health status of African populations that put groups at risk because of their increased susceptibility to Hg neurotoxicity. As recognized by Nweke and Sanders (2009), Africa's environmental health issues are complex; the environmental health policies and actions of the continent should be comprehensive, holistic, and population specific in the identification, recognition, and management of environmental health hazards. Additionally, the transition to addressing modern environmental health hazards in Africa is also occurring in other parts of the world that have a similar combination of pre-industrial and industrial era environmental health issues combined with the disease burden of children.

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José G. Dórea

Faculty of Health Sciences
Universidade de Brasília
Brasília, Brazil
E-mail: dorea@rudah.com.br

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