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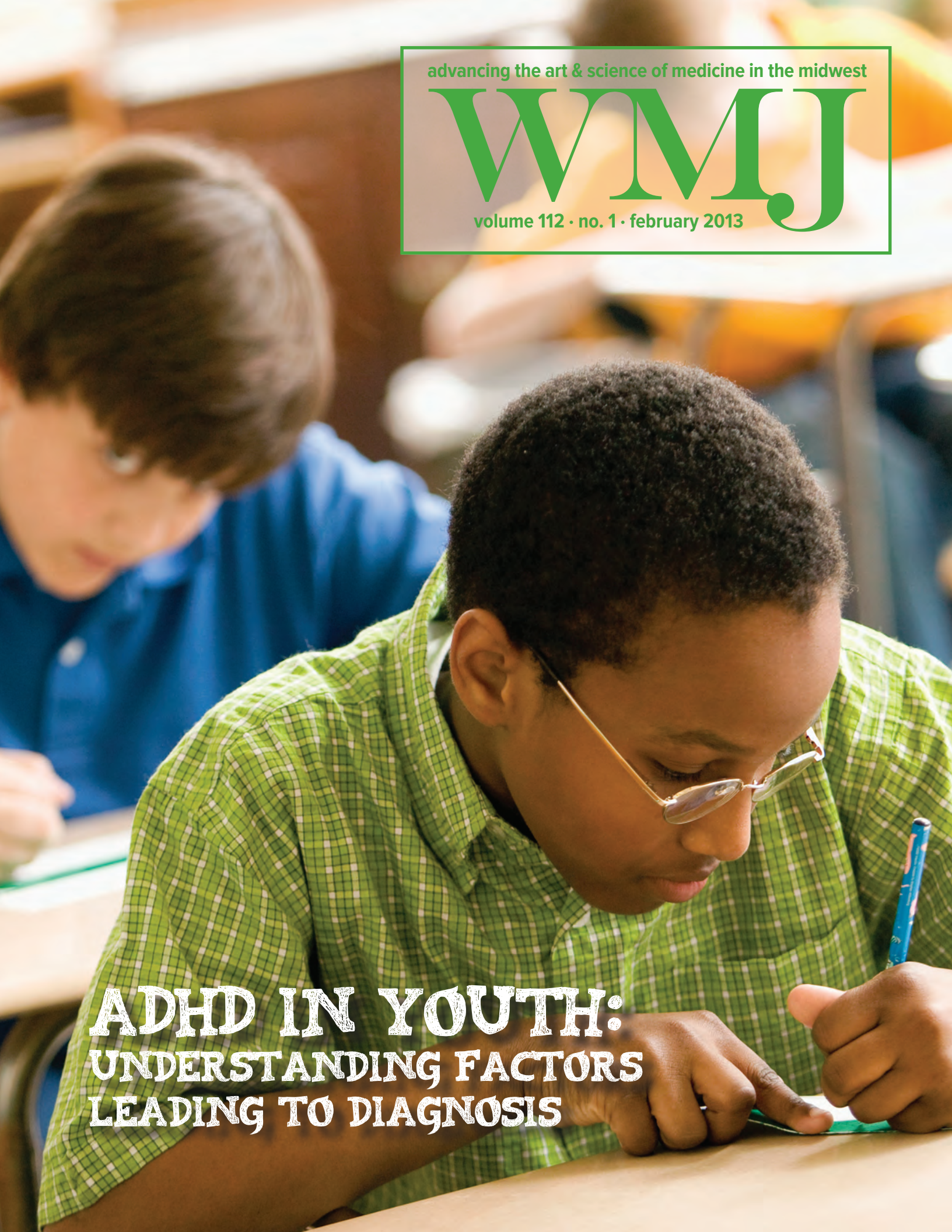

ADHD IN YOUTH: UNDERSTANDING FACTORS LEADING TO DIAGNOSIS

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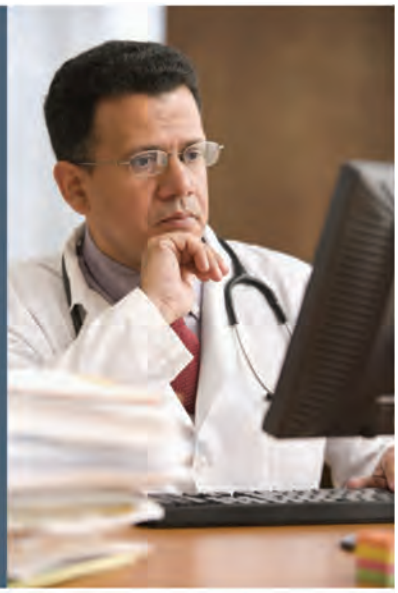

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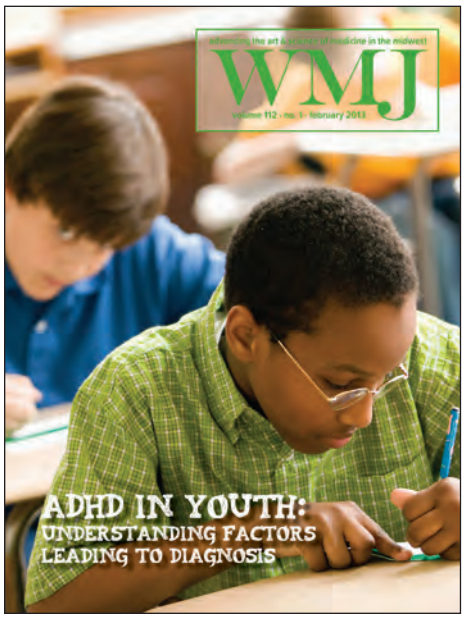

COVER THEME
ADHD in Youth: Understanding factors leading to diagnosis

Although both genetic and environmental factors have been implicated, the exact etiology of attention deficit/hyperactivity disorder is unknown. A study in this issue of *WMJ* explores sociocultural factors and disparities that may influence the diagnosis of ADHD in children. Better understanding of these influences can in turn lead to better treatment decisions and more informed stakeholders.

Cover design by Mary Kay Adams-Edgette.

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CASE REPORTS

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Mandatory Influenza Vaccine for Health Care Workers: 2012 Results

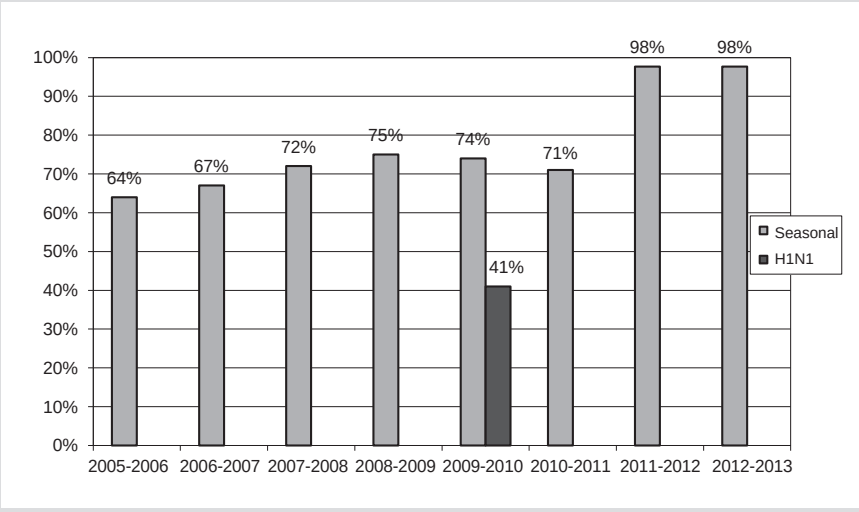
In the April 2012 edition, *WMJ*[1] published the initial results of a mandatory influenza vaccination program for employees of our health system. Many Wisconsin health providers have contacted us regarding our processes and inquired about our 2012 vaccination rates. I wish to share these, to allow health providers to consider this information if they are contemplating changes to their existing influenza vaccination programs.

Our 2012 employee vaccination rate and accepted exemption rates were identical with 2011. We again achieved a 97.7% vaccination rate, vaccinating 28,907 employees (Figure 1). We had a slight increase in medical and religious exemptions in 2012 (509) compared to 2011 (499; $P = 0.7$). Voluntary terminations of full-time or part-time employees decreased significantly from 11 to 2 ($P = 0.02$).

Two key changes were made in 2012. One was to move the deadline up to November 15, to avoid needing to make last-minute contact with clinicians and staff during the holiday season. This earlier deadline was easily met. The second major change was to add the requirement to credentialed medical staff, even if they were not Aurora employees. This affected over 1000 professionals, many of whom rarely if ever set foot within an Aurora facility. There were 27 physicians who chose to rescind their medical center privileges rather than provide evidence of vaccination.

The resources required to execute the second year of the vaccination policy were considered to be significantly less than the initial year. We feel the mandatory vaccination program is an acceptable process for us to accomplish our goal of creating a safe environment for patients and employees.

Figure 1. Percentage of Aurora Health Care Employees Receiving Influenza Vaccination During the 2005-2006 Through 2011-2013 Seasons.



David R. Smith, MD, MPH, Vice President, Patient Experience & Care Management, Aurora Health Care, Elm Grove, Wis

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Juvenile Delinquency

R.E. Bushong, MD, Milwaukee

Editor's note: The following was published in WMJ, *Volume 27 (No. 8), August 1928, p. 358.*

No trans-oceanic air flight brings more complications in charting the route than the effort to segregate the factors in a child offender's personality and environment that have resulted in his becoming a "juvenile delinquent." Through the Mental Hygiene Clinic, the Juvenile Court of Milwaukee County attempts such a diagnosis, so that the most intelligent remedy may be applied in each individual case.

Bad companionship stood out strikingly as the most potent single cause of misconduct among the environmental factors in the lives of the 300 children—208 boys and 92 girls—examined over a period of two years. In the 300 cases, 867 separate factors were found to be operating to produce delinquent behavior, an average of almost three to a child. Results in this group showed that in the average case there were present two environmental causes and one individual (personality) cause.

Cold figures point an accusing finger at the home life of these unfortunate youngsters. Unwholesome conditions in or pertaining to the home represent the largest group of factors in the environment of these boys and girls who have gone astray. Inadequate parental control occurred in 96 cases; bad home conditions (immorality, drinking, quarreling, abuse, crowding, etc) occurred in 84 cases; unhappy home life in 19, lack of parental understanding in 11. And so on down the line of unstable home conditions which seem inf1uential in causing a child to run counter to social rules.

Pursuing individual analysis into the more elusive mental factors, the results in the Mental Hygiene Clinic with this group of 300 indicates that mental defect has a great deal to do in predisposing a boy or girl toward delinquent conduct. In 126 out of 300 cases mental subnormality in some degree was a contributing factor.

Out of these 300 boys and girls it was found that 163, or 52.5 percent, had normal intelligence. Seventy-six, or 24 percent, fell into the subnormal group. Sixty-one, or 23.6 percent, were mentally defective. In the boys' group only 15.4 percent were defective, as against 31.5 percent in the girls' group. The clinic found that mental deficiency correlated pretty highly with sex offense among the girls seen. Mental defect in girls is not characterized by aggressive sex behavior so often as mentally deficient girls are apt to be easily suggestible victims of sex approaches. The boys involved in these cases are generally older and do not come within the jurisdiction of the Juvenile Court.

"Our figures tend to show, then, that the mentally diseased in any considerable number do not become delinquent unless environmental conditions are morally unfavorable. And those who hold that a strong casual [sic] relationship exists between mental disease as such and delinquency or crime will have to meet the challenge of the figures of our very carefully developed case studies in any of the four series, taken separately or comparatively."—Healy and Bronner, "Delinquents and Criminals—Their Making and Unmaking."

In exploring the inner mental life of the boys and girls examined, such important elements were found as inferiority feeling in 17 cases, mental conf1ict in 17, dynamic association in 4, grudge attitude in 3, theft ideation in 10, adolescent instability in 6, desire for recognition in 4, desire for possession in 9, desire for adventure in 8, desire for approbation in 1, and excessive imagination in 2.

Sex, as an instinctive urge in the individual life, makes for delinquency when the child cannot meet the issue adequately. This was brought out clearly in 34 cases, divided as follows: extreme sex ideation in 15 cases; early sex ideation or experience in 6; inadequate sex knowledge in 5; perverted sex ideation in 3; extreme sex curiosity in 3, and sex precocity in 2.

Thus it is seen that both the child and the environment need to be studied, the former in its physical and mental phases and the latter in its manifold aspects. Nothing less than a complete and comprehensive examination can hope to reveal all of the contributing inf1uences in juvenile delinquency, and it is only through their knowledge and revelation that effective treatment can be instituted.

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Understanding the 'What' Before the 'Why' in Population Research

John J. Frey, III, MD, Medical Editor

Sometimes replicating research in different populations clarifies our understanding of a health issue and at other times it creates many more questions than answers. In their previous study of attention deficit/hyperactivity disorder (ADHD) in Milwaukee County, Baumgardner et al[1] reported patterns of the diagnosis in populations that demonstrated racial and socioeconomic differences—higher frequency of diagnosis in white than African American boys and higher in less densely urban and more affluent areas of the county. By comparison, the Dane County data from Reyes and colleagues[2] in this issue of *WMJ* showed a higher rate of diagnosis in African American boys, while showing similar higher rates in more affluent and less densely populated parts of the county. However, the most disconcerting aspect of the Dane County study is that the overall rate of the diagnosis was almost 40% lower than that of Milwaukee County and 60% lower than the state overall. The question, of course, is why?

Medical care should be embarking on an era of fundamental reconsideration of many assumptions that underlie our current system of care, not the least of which is the belief that more is better. Whether it is data-driven analyses of PSA, mammography, the "annual physical," or diabetes that show no benefit, or worse, harm from too much screening or large studies of chronic diseases such as diabetes that show negative or no effect from more intensive management in the ACCORD studies,[3] more is not better; it is simply more—and more costly in many ways.

The diagnosis of ADHD includes the promise of "more"—whether that is primarily through drugs, many of which have unknown long-term consequences in children, or more intensive educational attention, which carries its own costs. Children who are labeled with the diagnosis of ADHD are more likely to become adults who carry that diagnosis and often are committed to a lifetime of medication. Reasons for the wide variability seen in the studies from Milwaukee and Dane counties has to include the attitudes of parents, school systems, physicians, and others who deal with children.

The most challenging and controversial components of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)—currently a bestseller on Amazon—have to do with what is and is not labeled as a mental disorder. Those controversies are unlikely to be resolved in our lifetime. Meanwhile, studies like that of Reyes and colleagues seem essential to identifying the profile of diagnoses and raising the issue of the complex relationship between social systems and health. The large health systems in the Upper Midwest offer an unusual opportunity to use the populations they care for to study and better understand the problem of what is labeled ADHD.

A report by Watkins and Watkins on the incidence of hematologic malignancies in rural and urban populations in south central North Dakota[4] also raises questions that require more research to understand and explain. They show that people who live in less densely populated areas of urban counties and those who live in rural counties both show a greater than expected rate of these malignancies, raising the question of environmental influences as one possible contributing factor. Years ago, a public health epidemiologist colleague said that attempts to show a relationship between exposure to high tension electrical lines and brain cancer ignored the reality that "we are bathed in a primal soup of electromagnetic radiation all the time." If that was true then, it is even more so now. Rural and urban populations are bathed in different "primal soups." The contribution by Watkins and Watkins calls for a more rigorous monitoring of the factors that make up our environment to understand how they affect our health. The wide open spaces have some very real risks, it appears.

Medical care should be embarking on an era of fundamental reconsideration of many assumptions that underlie our current system of care, not the least of which is the belief that more is better.

If you have cancer, are older than 60 and are involved in a clinical trial, you will have a lower level of informed consent than someone younger, without cancer. While Hoover-Regan and colleagues[5] report a high level of satisfaction by patients participating in clinical trials at an academic health center, they also confirm what many of us know both as clinicians and patients: there are physical, emotional, and social obstacles that demand that clinicians and research teams spend the time necessary to achieve truly informed consent.

Thanks to aggressive immunization of high-risk populations of young people and the military, meningococcal meningitis has become an historical footnote for many of us. While I saw it when I was first in practice 40 years ago, today it is truly a "reportable case." This issue of the *WMJ* contains an even more unusual case of the diagnosis of meningococcal meningitis in a newborn which, despite heroic measures by staff, resulted in the patient's death. The report of this case by Shah and colleagues[6] raises the concern that a now rare disease in adolescents may be less rare in younger children and infants. A 10-year review by Sotir and colleagues in the *WMJ* in 2005 confirmed the increasing trend for younger children.[7]

Finally, the case report from Kuy and colleagues[8] describes the complex surgical processes entailed by a sad case of self-inflicted injury. While the origin of the case may be unusual, the lessons learned are important for patients with combined anal and urinary injuries from whatever source.

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Edna at 15: Looking Back and Looking Ahead

Thomas D. Harter, PhD; Bernard J. Hammes, PhD

It has been 15 years since the Supreme Court of Wisconsin ruled in the matter of Edna.[1] Edna was a 71-year-old female who had advanced Alzheimer's dementia. She was bedridden, minimally responsive, and unable to feed herself. She received nutrition and hydration via a gastronomy tube. In 1995, Betty Spahn, Edna's sister and guardian, petitioned the Wood County Circuit Court to approve the discontinuation of Edna's nutrition and hydration based on her belief that Edna would not want to live in this condition. Edna never clearly indicated her preferences regarding life-sustaining treatment, or the continued provision of medically supplied nutrition and hydration. The petition was denied, and an appeal was then brought before Wisconsin's Supreme Court in 1997.

According to the higher Court, guardians in the state of Wisconsin cannot withhold or withdraw nutrition and hydration or other forms of life-sustaining treatment from wards who did not previously state their wishes regarding such treatments, or who are not in a persistent vegetative state (PVS). In this holding, the Court reaffirmed its 1992 ruling in the case of LW, maintaining that life-sustaining treatment, including nutrition and hydration, may be withheld or withdrawn from persons in PVS, since persons in this condition have no clear interest in or receive any benefit from such treatment, and do not sense things like pain, hunger, or thirst.[2] The Court also upheld the right of patient self-determination; if patients have clearly stated their preferences to forgo life-sustaining treatment, it is legally permissible not to offer or continue it.

In the Edna ruling, the Court stated that medically supplied nutrition and hydration is distinct from other kinds of life-sustaining treatment. While the Court cited public policy and an unwillingness to oppose the Wisconsin Legislature as its primary reasons for taking this view, it did not address why the general medical community treats nutrition and hydration as equivalent to other forms of life-sustaining treatment that, ethically, can be stopped if it fails to promote a patient's well-being through reversing a pathological process or relieving suffering. We consider the Court's failure to address the medical view of nutrition and hydration a serious flaw in the Edna ruling.

Some believe that the absence of nutrition and hydration necessarily causes hunger, thirst, or pain and suffering. However, this belief is not accurate for dying patients or patients with advanced dementia. Several medical studies and commentaries prior to the Court's ruling not only showed how forgoing medically supplied nutrition and hydration in dying patients does not cause thirst or hunger, but also how continuing this treatment contrasts with good comfort care at the end of life.[3-5] Research since Edna shows that medically supplied nutrition and hydration does not improve survival among patients with advanced dementia, and increases the risks of aspiration, pneumonia, and gastrointestinal discomfort.[6-10]

Some believe that the absence of nutrition and hydration necessarily causes hunger, thirst, or pain and suffering. However, this belief is not accurate for dying patients or patients with advanced dementia.

Since the Nancy Cruzan and Terri Schiavo cases in the 1990s, many medical organizations have issued statements on the administration and discontinuation of medically supplied nutrition and hydration.[11-14] Some positions are stronger than others. The American Academy of Neurology maintains that decisions about the use of nutrition and hydration should fall outside the scope of any state or federal oversight or judicial intervention. Common to these positions is the view that medically sup-

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Author Affiliations: Department of Medical Humanities, Gundersen Lutheran Medical Foundation, La Crosse, Wis (Harter, Hammes).

Corresponding Author: Thomas D. Harter, PhD, Associate Clinical Ethicist, Gundersen Lutheran Medical Foundation, C03-006B, 1900 South Ave, La Crosse, WI 54601; phone 608.775.0708; fax 608.775.1565; e-mail tdharter@gundluth.org.

plied nutrition and hydration often complicates the dying process without prolonging life. The majority state that substituted decisions about medically supplied nutrition and hydration must account for the net benefit to patients beyond their survival, and that physicians should not be obligated to provide nutrition and hydration when there is no predictable net benefit.

As a result of the Court's ruling, health care professionals in Wisconsin face ethical challenges every time they treat patients like Edna—ie, not in PVS and preferences about life-sustaining treatment are unclear or unknown. Consider the following hypothetical case: Baby J is a 3 year old who suffers an anoxic brain injury, leaving her comatose, but not meeting the diagnosis of PVS. After 2 months she is still comatose, not in PVS, but is now suffering from constant skin breakdowns and kidney failure. Her doctors believe that she has no reasonable medical probability of regaining cognitive functioning, and that her cognitive functioning is actually less than someone in PVS. Baby J's parents and doctors confer that they do not want to begin dialysis and want to transition to comfort measures only.

In cases like this, there is ethical justification for withholding and withdrawing life-sustaining treatment and transitioning to comfort measures only. Such justification typically hinges on a process of ascertaining medical judgments about the patient's current condition and predicted outcome, and working toward informed decision-making between the patient's family and the medical team(s) caring for the patient. The Edna ruling convolutes this process because the Court also failed to provide some necessary clarifications about what we should consider life-sustaining treatment, and whether the ruling should apply to non-PVS patients whose conditions are deemed neurologically worse than PVS. In lieu of these clarifications, health care professionals in Wisconsin may feel legally forced to provide any treatments capable of sustaining life to Edna-like patients, even when the treatments cannot cure or reverse their underlying medical conditions and may expose them to a variety of short-term and long-term harms and complications. Pediatric cases like Baby J's are particularly troublesome because there neither was nor will be an opportunity for neurologically devastated children to protest continued intervention in their unfortunate, yet inevitable, dying process.

As we look back on the Edna ruling, we appreciate and agree with the Court's principled stance toward wanting to protect vulnerable populations. Legal guardians and parents should not be allowed to decide that a ward's or child's life is not worth living simply because they have a diminished quality of life and be allowed to refuse medical treatment that would effectively treat the patient's medical conditions for this justification alone. As we look forward—considering how the ruling has affected decision-making over the past 15 years, and some of the implications of the ruling on future patients—we believe the Court should consider 3 additional ways to help health care professionals in Wisconsin. First, we would ask the Court to reconsider its inaccurate view of medically supplied nutrition and hydration as a treatment distinct from other forms of life-sustaining treatment. Second, the Court should clarify and define life-sustaining treatment to mean only effective treatments that are capable of reversing a pathological process or offering some sort of net benefit to patients. For example, cardiopulmonary resuscitation is a type of life-sustaining treatment, but for some patients with serious, advanced conditions it has no chance of preventing their death in the near or immediate future, and its attempt could inflict serious harm. Lastly, we want the Court to clarify for health care professionals when treatments that have some small chance of extending life, but also inflict significant pain and suffering, may be forgone by legal guardians and parents.

These requests for clarifications actually mirror the definition of "withholding of medically indicated treatment" and the exceptions to continuing life-sustaining treatment in infants and children under the Child Abuse and Neglect Prevention and Treatment Program by the Department of Health and Human Services.[15] By not addressing these 3 points, the Supreme Court of Wisconsin leaves health care professionals and families to navigate the murky boundaries of the Edna ruling, where missteps really are a matter of life and death.

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The Potential for Sociocultural Factors in the Diagnosis of ADHD in Children

Noemi Reyes; Dennis J. Baumgardner, MD; David H. Simmons, MPH; William Buckingham, PhD

ABSTRACT

Purpose: The nongenetic contributors to attention deficit/hyperactivity disorder (ADHD) remain to be identified. A previous study in eastern Wisconsin (prevalence 13.5%) suggested that male gender, white race, lower block group median household income and population density, and greater distance to the nearest park were factors predictive of ADHD diagnosis. We performed a similar study in Dane County, Wisconsin.

Methods: Cross sectional study of children age 5-17, with and without ADHD diagnosis, who received well child care in Dane County UW Family Medicine clinics (N=7954) 2007-2008. Street addresses were geocoded to 2000 Census block group. Univariate analysis was done by chi-square test or Mann-Whitney U test, multivariate analysis by logistic regression.

Results: ADHD diagnosis was present in 309 (3.9%) children (74.1% male; $P = 0.000$, compared to females) and more frequently diagnosed in black children (6.8% of black children had ADHD diagnosis) than white (4%), Native American (2.7%), Hispanic (1.6%), or Asian (1.3%) children. In contrast to eastern Wisconsin and to Milwaukee County (a subset of the eastern Wisconsin study where black rates were identical to that of Dane County), black race rather than white race was predictive of ADHD in Dane County, while median household income, population density, and distance to nearest park were not associated. The range of ADHD within school district boundaries was 2.4%-7.1% (for N>100/district). In the group of districts with >4% ADHD diagnosis, the increased rates were largely among whites.

Conclusion: ADHD diagnosis was much less common in this Dane County cohort than in eastern Wisconsin and was more common among blacks, but not predicted by other geo-demographic factors. Like eastern Wisconsin, ADHD diagnosis prevalence varied with apparent school district boundaries.

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that manifests in childhood. The exact etiology is unknown, but both genetic and environmental factors traditionally have been implicated.[1] Some have found little support for a biomedical model for ADHD and there is controversy regarding the consideration of this diagnosis as solely or partially a cultural or social construct.[2-5] A number of sociocultural, access, payment, and provider-related factors also help determine rates of ADHD diagnosis.[6-11]

The mean prevalence rates for parent-reported ADHD diagnosis in the United States among children ages 4-17 in 2007 was 9.5% (95% CI: 9.0-10.0) (9.9% in Wisconsin; range among states, 5.6%-15.6%). Rates in this study[12] were not statistically different between white (9.9%) and black (10.1%) children, but differed between Hispanic (5.6%) and non-Hispanic (10.5%) children. Rates were increased with lower income, based on poverty level.

A recent study (data from August 16, 2004 to August 15, 2006) of 6833 eastern Wisconsin children with ADHD diagnosis and 43,630 controls revealed that ADHD was diagnosed more frequently in white children (17.3%) than in blacks (10.6%), Hispanics (9.4%) or Asians (3.7%). Overall, male gender, white race, lower block group median household income and population density, and greater distance to nearest park were more predictive of ADHD. Rates appeared to vary by school district boundaries. Similarly, in urban Milwaukee County (865 cases/10,493 controls) male gender, white race, suburban residence, and younger age were more predictive of ADHD.[6]

If findings in Dane County were to confirm the geographic and demographic disparities found in this previous work, they would strongly favor a sociocultural model of ADHD in Wisconsin, and call for reflection upon the basis for, and implications of, a diagnosis of ADHD. By better understanding factors and disparities leading to a diagnosis of ADHD (whether socioeconomic, racial/ethnic, environmental, or issues of access), bet-

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Author Affiliations: University of Wisconsin–Milwaukee (Reyes); Department of Family Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wis (Baumgardner, Simmons); Aurora UW Medical Group/Center for Urban Population Health, Milwaukee, Wis (Baumgardner); Applied Population Laboratory, Department of Rural Sociology, University of Wisconsin–Madison (Buckingham).

Corresponding Author: Dennis J. Baumgardner, MD, Center for Urban Population Health, 1020 N 12th St, Ste 4180, Milwaukee, WI 53233; phone 414.219.5191; fax 414.219.3116; e-mail dennis.baumgardner@fammed.wisc.edu.

Table 1. Demographic Data: Children with Attention Deficit/Hyperactivity Disorder (ADHD) vs Controls, All Dane County Subjects, Madison Metro Subset, and Dane County Subsets of School Districts with ADHD Diagnosis Prevalence <4% and >4%

	Dane County		Subset: Madison Metro		Subset: ADHD < 4%		Subset: ADHD >4%	
	ADHD No. (%)	Controls No. (%)	ADHD No. (%)	Controls No. (%)	ADHD No. (%)	Controls No. (%)	ADHD No. (%)	Controls No. (%)
Gender								
Male	229 (74)[a]	3675 (48)	46 (79)[a]	855 (45)	92 (74)[a]	1923 (47)	137 (74)[a]	1750 (49)
Female	80 (26)	3970 (52)	12 (20)	1011 (54)	33 (26)	2159 (53)	47 (26)	1811 (51)
Race/Ethnicity								
White	247 (80)	5984 (78)	25 (43)	960 (51)	87 (70)	2917 (71)	160 (87)	3065 (86)
Black	46 (15)	629 (8)	29 (50)	402 (22)	33 (26)	471 (12)	13 (7)	158 (4)
Hispanic	7 (2)	420 (5)	2 (3)	214 (11)	2 (2)	294 (7)	5 (3)	126 (4)
Native American	1 (0)	36 (0)	0 (0)	13 (1)	0 (0)	25 (1)	1 (0)	11 (0)
Asian	4 (1)	303 (4)	2 (3)	195 (10)	2 (2)	247 (6)	2 (1)	56 (2)
Other	0 (0)	8 (0)	0 (0)	2 (0)	0 (0)	2 (0)	0 (0)	6 (0)
Unknown	4 (1)	265 (3)	0 (0)	80 (4)	1 (1)	126 (3)	3 (2)	139 (4)
Age								
Mean	11.47	11.45	11.36	11.80	12.30	11.40	11.70	11.50
Median	12.00[b]	12.00	11.50	11.00	12.00	12.00	11.50	12.00

All percentages refer to the percentage of the column subset for that numerical value.
All *P*-values refer to the comparison of ADHD cases vs their respective controls, within each set or subset.
[a] $P<0.001$
[b] $P<0.05$

Table 2. Attention Deficit//Hyperactivity Disorder (ADHD) Prevalence Rates Within Race/Ethnic Groups

	Dane County No. (%)	Madison Metro No. (%)	ADHD<4% Districts No. (%)	ADHD>4% Districts No. (%)
White	247 (4.0)	25 (2.5)	87 (2.9)	160 (5.0)[c]
Black	46 (6.8)[a]	29 (6.7)[a]	33 (6.6)[a]	13 (7.6)
Hispanic	7 (1.6)[b]	2 (0.9)	2 (0.7)[b]	5 (3.8)
Native American	1 (2.7)	—	—	1 (8.3)
Asian	4 (1.3)[b]	2 (1.0)	2 (0.8)	2 (3.5)
Unknown	4 (1.5)	—	1 (0.8)	3 (2.1)

[a] $P<0.001$, compared to white in respective column
[b] $P<0.05$, compared to white in respective column
[c] $P<0.001$, compared to white in ADHD <4% districts

ter decisions regarding appropriate treatment can be made and families, health care workers, educators, funders, and policy makers be better informed.

METHODS

Setting

Dane County is located in south-central Wisconsin and by US Census Bureau 2011 estimates has a population of 495,959 (82% white, 5% black, and 6% Hispanic). The median household income is $60,519 and 45% of persons 25 or older have a bachelor's degree or higher. Madison is the largest city, with a population of 236,901 (76% white, 7% black, and 7% Hispanic), a median household income of $52,550 and 52% with a bachelor's degree or higher. By comparison, Milwaukee County, located in southeastern Wisconsin, has a population of 952,532, is 54% white, 27% black, and 14% Hispanic, and has a median household income of $43,215 and a rate of 27% with a bachelor's degree or higher.

Data and Analysis

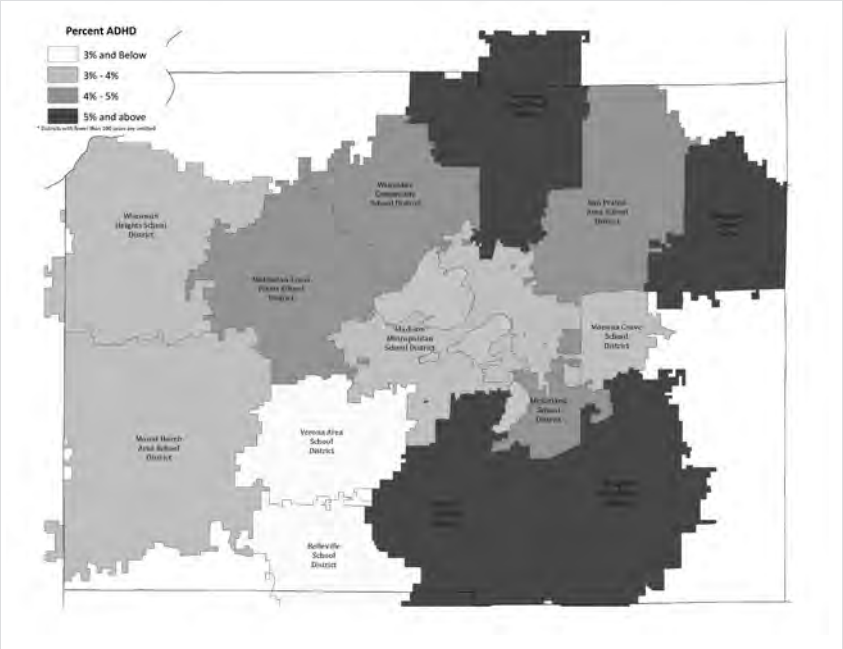
The general methods were similar to that of the previous work.[6] The study population was assembled from a data warehouse, which included all 22 University of Wisconsin Department of Family Medicine community clinics in Dane County, Wis. Subjects included all Dane County children ages 5-17 who received well child care in these clinics in calendar years 2007 and 2008 (N = 7954). Cases included those with the diagnosis ADHD (ICD-9 codes 314.0 – 314.9) at any encounter during the study period. Control subjects included all children in this age range without ADHD diagnosis. As in our previous study,[6] it must be emphasized that this was a study of potential disparities regarding ADHD *diagnosis* as captured by billing codes.

Demographic data was geocoded and mapped using ArcGIS (Esri; Redlands, CA). Individual data obtained for each subject included age, street address, and race/ethnicity. US Census 2000 block group level demographic, population density, median household income, percent owner-occupied housing, and average household size data was linked to each subject by street address. In addition, school district assignment and distances to nearest park and waterway were determined for each home address. Statistical analysis was performed with the assistance of MINITAB software (Minitab; State College, PA). Normality tests utilized the Anderson-Darling method. A chi-square test (with Yates correction for 2 x 2 tables) or 2-tailed Fisher exact test was used for categorical data and *t* tests (normally distributed) and

the Mann-Whitney U test (non-normally distributed) were utilized for comparison of continuous variables. P values < 0.05 were considered statistically significant. Multivariate analysis was performed utilizing binary logistic regression models that included age, gender, race/ethnicity category and any variable which was statistically significant in univariate analysis.

This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board.

Figure 1. Geographic Distribution of Attention Deficit//Hyperactivity Disorder (ADHD) Diagnosis Among Dane County School Districts



RESULTS

Table 1 summarizes demographic comparisons of children diagnosed with ADHD and controls. Of the 7954 children included in the entire study population, the mean and median age was 11.5 and 12.0 years, respectively. Using the same age groupings as in the Centers for Disease Control and Prevention (CDC) report[12] (except our study did not include 4 year olds), there was a non-significant increase in ADHD diagnosis prevalence with increasing age group: ages 5-10, 3.6%; 11-14, 4.0%; 15-17, 4.1% (P-values > 0.4 for all group comparisons). Overall, 4050 (50.9%) of the study population were female, and the race/ethnicity breakdown was as follows: white, 6231 (78.3%); black, 675 (8.5%); Hispanic, 427 (5.4%); Asian, 307 (3.9%); Native American, 37 (0.5%); and unknown/other, 277 (3.5%). ADHD diagnosis was present in 309 (3.9%) children (74.1% male; $P = 0.000$, compared to females) and within the study population was more prevalent among black children (6.8%) than white (4%; $P < 0.001$), Hispanic (1.6%; $P < 0.001$), Asian (1.3%; $P < 0.001$) or Native American (2.7%; $P = 0.5$) children. All statistical comparisons are to black children. In contrast to eastern Wisconsin,[6] where white race was predictive of ADHD diagnosis, in Dane County black race was predictive of ADHD.

The first column of Table 2 lists Dane County ADHD prevalence rates among race/ethnicity groups, with white children as the comparison group.

Median household income, population density, and distance to the nearest park were not associated with ADHD diagnosis in Dane County by univariate analysis (Table 3).

The range of ADHD diagnosis within school district boundaries was 2.4%-7.1% (for districts with > 100 subjects/district); however, there was not an obvious geographical distribution pattern, except that all districts with $> 4\%$ ADHD rates were suburban districts (Figure 1).

The study population was divided into several subsets, the first of which was Madison Metropolitan School District, which is the most urban area of Dane County (Tables 1 and 2). Within this subset, the population had an ADHD prevalence of 3.0% with more frequent diagnosis in black children (6.7%) compared to white children (2.5%; $P < 0.001$). There were no significant differences in linked population density, median household income, percent owner occupied housing, household size, or household distance to nearest park or waterway, when comparing children with ADHD diagnosis to controls (Table 3).

The entire study population was then divided into subsets by school district boundaries with ADHD diagnosis prevalence $> 4\%$ and $< 4\%$ (Tables 1 and 2).

In school districts with rates $< 4\%$, the prevalence was 2.9% among white children and 6.6% among black children ($P < 0.001$). In the >4% subset, prevalence among white children increased to 5.0% ($P < 0.001$, compared to white children in the <4% subset), while no significant increase in prevalence was demonstrated among black children (7.6%; $P = 0.8$, compared to black children in the $< 4\%$ subset). Small numbers of subjects in these subgroups prohibited meaningful comparisons of race/ethnic groups other than black or white. Although the total number of black children within the $> 4\%$ districts was considerably lower (Table 1), the rate of ADHD diagnosis among black children remained similar to the $< 4\%$ group ($P = 0.8$, as above), despite sociodemographic differences between the 2 groups of school districts.

Table 4 lists individually linked geographic and US Census sociodemographic data for Dane County school districts with

Table 3. Individually Linked Geographic and Census-Derived Sociodemographic Data: All Subjects and Madison Metropolitan School District Only

	Dane County		Subset: Madison Metro	
	ADHD (Median)	Controls (Median)	ADHD (Median)	Controls (Median)
Population density (persons/square mile)	692.2	741.0	4,391	4,119
Median household income ($)	60,136	60,136	44,531	47,219
Percent owner occupied housing	0.74	0.76	0.48	0.59
Average household size	2.63	2.63	2.36	2.34
Distance to nearest park (miles)	0.63	0.66	0.56	0.53
Distance to nearest waterway (miles)	0.41	0.43	0.40	0.40

Abbreviation: ADHD, Attention deficit/hyperactivity disorder
No comparisons between ADHD cases and controls were statistically significant (all *P* values > 0.23).

Table 4. Individually Linked Geographic and Census-Derived Sociodemographic Data: Dane County School Districts with ADHD Prevalence < 4% vs School Districts with ADHD Prevalence > 4%

	ADHD < 4% Districts		ADHD > 4% Districts	
	ADHD (Median)	Controls (Median)	ADHD (Median)	Controls (Median)
Population density (persons/square mile)	975.5	975.5	473.8	457.7
Median household income ($)	55,536	55,385	60,294[a]	61,932
Percent owner occupied housing	0.74	0.74	0.75	0.78
Average household size	2.57	2.54	2.72	2.76
Distance to nearest park (miles)	0.68	0.71	0.54	0.57
Distance to nearest waterway (miles)	0.47	0.45	0.40	0.42

Abbreviation: ADHD, Attention deficit/hyperactivity disorder
[a]*P* < 0.05, ADHD cases, compared to control, districts with ADHD prevalence > 4%.

ADHD prevalence < 4% vs school districts with > 4% ADHD prevalence. In the > 4% subset only, linked median household income was lower among those with ADHD diagnosis than without this diagnosis ($60,294 vs $61,932; $P < 0.05$); however, in a multivariate logistic regression model including age, gender, and race/ethnicity, this variable was not significant ($P = 0.095$). For all subjects (cases and controls) in school districts with ADHD diagnosis prevalence > 4%, there was significantly lower population density (458 vs 976), higher median income ($61,932 vs 55,385), higher percent owner occupied housing (0.78 vs 0.74), and increased household size (2.76 vs 2.54). All *P*-values < 0.001 compared to districts with < 4% prevalence; however, the absolute differences in the latter 2 comparisons were small.

DISCUSSION

The overall prevalence of ADHD diagnosis in this Dane County, Wisconsin cohort of children ages 5-17 was 3.9%. This figure is substantially lower than that reported for the entire state of Wisconsin for children 4-17 (9.9%), based on parental report in a national survey,[12] and that previously reported for eastern Wisconsin (13.5%), based on clinical billing data of children seen in primary care clinics.[6] This was despite the Dane County data reflecting a period an average of 17 months later than of the eastern Wisconsin cohort, at a time when national rates were increasing.[12] ADHD diagnosis was most prevalent among black children in Dane County, but not predicted by other individually linked sociodemographic factors. Similar to the eastern Wisconsin cohort, ADHD diagnosis prevalence varied with apparent school district boundaries. In addition, lower population density (similar to eastern Wisconsin) and higher median income typified the higher prevalence rate school district subgroup in the present study. The Dane County data also may be compared to the Milwaukee subset of the previous study.[6] In Dane County, the prevalence of ADHD diagnosis among black children was 6.8%, the same as was seen in the Milwaukee county subset. In contrast, the prevalence among white children in Dane County was 4.0%, but was 12.6% in Milwaukee County.[6]

In Dane County school districts with ADHD prevalence > 4.0% the total number and percentages of black children residing within these districts was considerably lower, but the prevalence was non-significantly higher compared to the < 4.0% subset, while the rates of white children were significantly increased.

Taken together, these findings suggest that families in certain school districts or suburban areas may be more likely to get an ADHD diagnosis for their children than families in an urban setting. Obviously, there are many possible explanations for this finding, including geographic differences regarding adequacy of medical home and insurance coverage, clinician diagnostic habits and use of ADHD diagnostic codes, cultural and school district norms, and parental involvement, expectations and aggressiveness in seeking ADHD diagnosis for their children with poor school performance, as discussed in previous reports.[3-7,9-11,13,14]

One explanation for the remarkably lower Dane County prevalence (3.9%), compared to Milwaukee County (7.7%), and the City of Milwaukee (6.6%) could be a difference in school-based infrastructure available to assist in diagnosis of ADHD. Information provided by the various Dane County school districts in July 2011 revealed that some Dane County school districts appoint 1 psychologist to a maximum of 4 schools, while others may have 1 per school. All of the schools follow a procedure that includes a coordinated effort where the parents, school

psychologist and a physician share information to come to a diagnosis or verify an existing diagnosis and treatment. Overall, there were 172 schools and 102 full- and part-time psychologists among the Dane County school districts. This ratio did not vary much among the districts and did not seem to explain the higher ADHD prevalence rates among school districts with > 4% ADHD rates. Similar data from Milwaukee Public Schools revealed that 184 schools shared 158 psychologists. There was no data regarding the proportion of part-time psychologists, or clinician-school coordination. Resources, philosophy, coordination and access to care, parent availability for appointments, and completion of specialist referrals may be contributing factors to ADHD prevalence rates in particular school districts.

This study has several weaknesses. The data includes only children from 1 group of UW Family Medicine clinics, and has a relatively low sample size for certain subset analyses. Like the previous study in eastern Wisconsin,[6] our data was limited to the information in diagnostic codes for encounters during the study time period, and does not include information on whether the ADHD diagnosis originated with the practitioner or a specialist, or if the diagnosis was validated. The data was not analyzed for co-existing behavioral disorders or sleep disorders, and does not include clinical data from specialists or school psychologists. These are weaknesses in both studies; however, the assumptions and methods of data collection were similar in both studies, suggesting usefulness of comparison.

In summary, ADHD diagnosis rates were significantly lower in this Dane County cohort than reported for eastern Wisconsin, but were similarly varied by school district boundaries. While diagnosis rates among blacks were similar between the 2 counties, rates for whites were 3 times lower in Dane County than Milwaukee County. Further studies are needed to determine if such differences exist among large communities in other states, and if regional and cultural family expectations, school resources and communications, diagnostic practices, community education, or other factors explain these disparities. Clinicians would be well served to be aware of regional differences in ADHD diagnosis prevalence, and the potential underlying sociocultural constructs, when entertaining or questioning the diagnosis of ADHD in children in their practice.

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Informed Consent and Research Subject Understanding of Clinical Trials

Margo Hoover-Regan, MD; Tara Becker, PhD; Mary Jane Williams, MPH, BSN; Yoram Shenker, MD

ABSTRACT

Context: Current evidence suggests many clinical trial participants have incomplete understanding of research objectives and methods.

Objective: Determine consent standards compliance, satisfaction with facility and study staff, and research subject understanding of clinical trials.

Design: Retrospective review of responses gathered when subjects were interviewed at the inception of clinical trial participation.

Setting: Clinical research unit at the University of Wisconsin, Madison.

Patients: Clinical trials participants on the research unit.

Main Outcome Measures: Understanding of the particular trial in which each subject was participating; research team compliance with informed consent standards; and satisfaction with the research facility, staff, and clinical trials teams.

Results: 423 of 570 research participants were oncology patients; 298 were males. Age range was 10 to 90 years old (mean of 56.6 (+/-16.6) years old). Most subjects (99%) had signed the consent form; 97% reported satisfaction with the research facility and 96% with the study staff. Four-fifths of participants had accurate knowledge of study aims, methods, and risks, but 20% of subjects understood considerably less. Oncology subjects were older (mean age 60.1 [+/-12.5] years vs 46.4 [+/-21.9] years, $P < 0.001$). Non-oncology subjects and patients under age 61 demonstrated superior study knowledge ($P < 0.001$).

Conclusion: Compliance with informed consent standards and satisfaction with services and staff was excellent. Future efforts should focus on better informing older subjects and those on oncology trials.

INTRODUCTION

In 2001, the National Institutes of Health (NIH) introduced the requirement of having a Research Subject Advocate (RSA) in every federally funded General Clinical Research Center (GCRC). The primary function of the RSA is to ensure that studies are designed and conducted safely and ethically with protection of human subjects accorded the highest priority. The University of Wisconsin GCRC, a unit of 15 inpatient and 6 outpatient rooms, appointed its first RSA in the fall of 2001. Within the first 6 months, the advocate developed several initiatives aimed at enhancing subject safety and supervising compliance with research regulations and ethical conduct. A quality control initiative was implemented in which a checklist was used to assess individual patient understanding and study staff adherence to informed consent standards. This assessment was done by administering a checklist via a face-to-face interview. This was initially done 3 days per week, and after the addition of a second advocate in September 2006, patients were interviewed on all 5 weekdays. The data were collected from February 2005 through August 2009.

METHODS

Research subjects were interviewed by an advocate, a nurse manager, or both at the inception of participation in a clinical study. On occasion, the same patient was enrolled in a second trial and the data from this separate interview were also included. Typically 1 to 3 patients were seen per day. On less than 10% of the days, there were no new participants to interview. Interviews lasted approximately 5 to 10 minutes.

The checklist contained the following identifying items: room number, participant's initials, age, gender, diagnosis, treatment, and study identification number and title. These items were pre-filled by the nurse manager or charge nurse. Subjects were interviewed individually, and were first asked how they had learned about the study (eg, via their treating physician, a flier,

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Author Affiliations: University of Wisconsin School of Medicine and Public Health Clinical and Translational Research Core, Department of Pediatrics (Hoover-Regan); Department of Biostatistics (Becker); Department of Medicine (Shenker); University of Wisconsin Hospital and Clinics (Williams).

Corresponding Author: Margo Hoover-Regan, 1111 Highland Ave, Rm 4109, Madison, WI 53705-2275; phone 608.263.6200; fax 608.265.9721; e-mail mhooverregan@pediatrics.wisc.edu.

or advertisement). Protocol knowledge then was assessed. The leading question usually was, "What is your understanding of the research study?" followed by more specific questions. In a few cases (estimated at less than 10%), responses provided by a spouse or significant other were accepted in addition to those offered by the subject.

The subject's study knowledge was rated based upon the following 4 criteria: (1) expressed full familiarity with the procedures and medication; (2) included the mechanism of action of the study drug; (3) demonstrated knowledge of research study goals; and (4) had complete knowledge of side effects. Knowledge was rated as excellent if the interviewee answered affirmatively to all 4 data elements; very good if 1 to 2 elements were omitted (most typically this was the mechanism of action of a study drug); fair if 3 elements were omitted; and poor if none of these elements was mentioned.

Subjects were asked if they had been given a signed copy of the consent form and study staff contact information. They also were asked to rate the consent process as appropriate or inappropriate, based on whether or not they felt sufficient information had been provided to allow them to decide if they wanted to participate in the study.

Patient satisfaction with the research unit staff and environment, and the research investigator's team, was rated as high, moderate or low. Additional comments related to these 2 queries, quoted verbatim from the respondents, also were recorded frequently.

Data were analyzed by calculating descriptive statistics for the full sample, by study type (oncology vs nononcology), and gender (male vs female). Differences between groups for categorical variables (eg, study knowledge) were tested using the non-parametric Fisher's exact test. Differences between groups for continuous variables (eg, age) were tested using variance analysis.

The study received an exemption for the need for consent from the University of Wisconsin Health Sciences Institutional Review Board.

RESULTS

Over the period covered in this analysis, 2364 subjects were admitted to the research unit and interviews were conducted with a random sample of 570 research participants (24%). Table 1 shows the descriptive statistics for all patients interviewed. Age ranged from 10 to 90 years.

Table 2 compares oncology study participants to nononcology study participants. The mean age of the oncology study participants was 60.1 (+/- 12.5) years, while the mean age of nononcology study participants was 46.4 (+/- 21.9) years. This difference was statistically significant ($P < 0.001$). Oncology study participants were more likely to be male (57%) compared to nononcology study participants (38%), and this difference was statistically significant ($P < 0.001$).

Table 1. Descriptive Statistics—Full Sample

	N	All Mean/%	SD
Age	**570**	**56.57**	**16.61**
Year of visit			
2005	57	10.3	
2006	154	27.9	
2007	141	25.6	
2008	130	23.6	
2009	69	12.5	
Gender			
Male	298	52.4	
Female	271	47.6	
Type of study			
Oncology	423	74.2	
Nononcology	147	25.8	
Knowledge of study			
Excellent	195	34.6	
Very Good	264	46.9	
Partial	102	18.1	
None	2	0.4	
Consent			
No	5	0.9	
Yes	554	99.1	
Consent process was appropriate			
Appropriate	563	99.8	
Inappropriate	1	0.2	
Satisfaction with CTRC			
High	537	96.9	
Moderate	17	3.1	
Low	0	0.0	
Satisfaction with research staff			
High	533	95.9	
Moderate	22	4.0	
Low	1	0.2	

Abbreviation: CTRC, Clinical and Translational Research Core

Nononcology study participants showed better study knowledge ($P < 0.001$).

Figure 1 shows the probabilities of reporting Excellent, Very Good, or Partial/None study knowledge by age for the oncology participants. Figure 2 shows these probabilities for the nononcology participants. Overall, oncology study participants showed less research study knowledge than non-oncology study participants ($P = 0.001$). The study knowledge was lower among the youngest subjects and then increased until about age 39 before declining among older participants, such that subjects who were older than age 68 had less knowledge about the research study than the youngest subjects.

As shown in Table 3, there were few differences by gender. With respect to age, the 20- to 40-year-old patients were far more likely to be on oncology studies than nononcology studies

Table 2. Descriptive Statistics by Study Type, with Fisher's Exact Test *P*-values

	Oncology			Nononcology			
	N	Mean/%	SD	N	Mean/%	SD	*P*-value
Age	**423**	**60.11**	**12.53**	**147**	**46.37**	**21.93**	**<0.001**
Year of visit							**<0.001**
2005	52	12.8		5	3.5		
2006	123	30.2		31	21.5		
2007	86	21.1		55	38.2		
2008	91	22.4		39	27.1		
2009	55	13.5		14	9.7		
Gender							**<0.001**
Male	242	57.3		56	38.1		
Female	180	42.7		91	61.9		
Knowledge of study							**<0.001**
Excellent	129	31.0		66	44.9		
Very good	196	47.1		68	46.3		
Partial	89	21.4		13	8.8		
None	2	0.5		0	0.0		
Consent							**0.219**
No	5	1.2		0	0.0		
Yes	408	98.8		146	100.0		
Contact information							**0.426**
No	6	1.4		1	0.7		
Yes	413	98.6		144	99.3		
Consent process was appropriate							**0.743**
Appropriate	418	99.8		145	100.0		
Inappropriate	1	0.2		0	0.0		
Satisfaction with CTRC							**0.142**
High	396	96.4		141	98.6		
Moderate	15	3.6		2	1.4		
Low	0	0.0		0	0.0		
Satisfaction with research staff							**0.142**
High	392	94.9		141	98.6		
Moderate	20	4.8		2	1.4		
Low	1	0.2		0	0.0		

Abbreviation: CTRC, Clinical and Translational Research Core

(65% vs 35%), while patients who were ages 41 and over were far more likely to be on nononcology studies (81% of those ages 41 to 60 years and 83% of those over age 60). This difference was statistically significant ($P<0.001$). The relationship between age and study knowledge seen in Figures 1 and 2 can also be seen in Table 4: patients under age 61 are more likely to have excellent or very good study knowledge than patients over age 60 (90% vs 73%). This difference is statistically significant ($P<0.001$). The vast majority of the 217 comments about level of satisfaction with the research unit and study staff were very positive, particularly toward the research unit nurses. Thirty-three comments were negative, most of which were related to delays in starting chemotherapy.

DISCUSSION

The Declaration of Helsinki (1964) and the Belmont Report (1979) established worldwide and national ethical guidelines for human subject research. Ensuring that clinical trials participants are informed of clinical trial goals, benefits, potential risks, methods, and provided the right to choose or refuse participation are key tenets of both documents. However, the declaration fails to define adequate understanding of informed consent. Our report focuses on an institution's efforts to evaluate clinical trials subjects' understanding of these elements, study staff compliance with policies aimed at achieving optimal subject understanding, and subject satisfaction with certain aspects of clinical trial participation.

With the goal of maximizing subjects' comprehension of clinical trials and, in turn, promoting patient/participant autonomy, consent form standards have become quite rigorous and language in the resulting documents is often complex. The content of these complicated forms typically is explained to the potential participant by a member of the research team who is well versed in the methods, risks, benefits, and alternatives to participation in the trial. In theory, this can result in good understanding of the issues at hand and autonomous, truly informed consent, but barriers definitely exist. The potential subject's education level, physical health, and prognosis are but a few factors which might impede comprehension. Furthermore, if the reading level of the form is too high, the subject may not have a realistic chance of understanding the content. Federal regulations are in place to protect patients with diminished cognitive and decision-making capacity; in such situations, the burden of comprehension and weighing risks and benefits may fall on a surrogate or representative.

In an effort to evaluate the effectiveness of the consent process, various methods have been used to assess subjects' understanding of the clinical trials in which they are participating. Specifically, subjects have been interviewed or asked to complete questionnaires. Some investigators have used instruments that rely on self report; that is, participants are asked whether or not they understand aspects of the trial (and sometimes they are also asked to rate the degree of understanding).[1-3] In the majority of studies, however, the investigators themselves determined the level of subjects' comprehension, either by asking open-ended questions in

Figure 1. Predicted Probability for Level of Knowledge about the Study by Age: Oncology

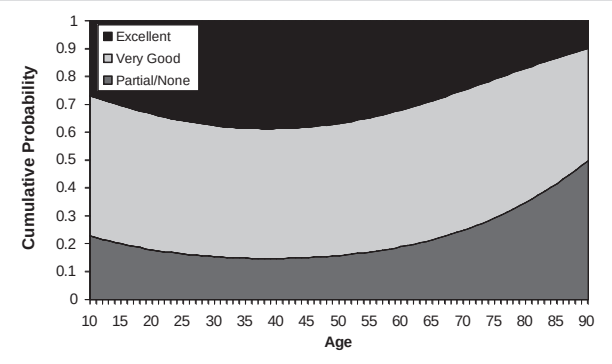
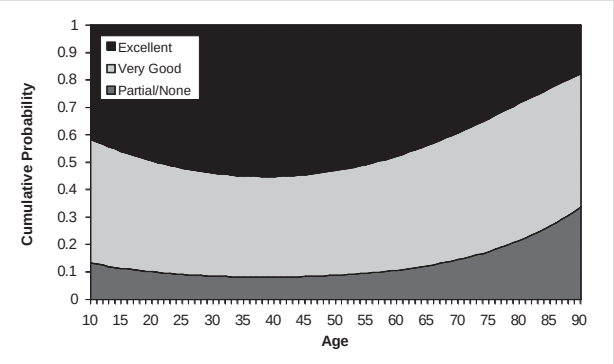


Figure 2. Predicted Probability for Level of Knowledge about the Study by Age: Nononcology



an interview format, focused questions about specific aspects of a clinical trial, or a combination of these 2 types of queries.[4-9] Rarely, these tools have been validated. For example, one study assessed subject understanding of 3 Eastern Cooperative Oncology Group trials via telephone interviews in which participants were asked 23 true/false and multiple-choice questions that had been judged to have high content validity by a panel of experts.[10] While the questions we asked in the current study were not validated, the interviewers thoroughly reviewed each protocol monograph in advance in order to make as accurate a determination as possible of the subject's understanding of the clinical trial.

Despite the existence of policies and rigorous federal guidelines for informed consent in research, subjects' understanding of their clinical trials is often inadequate. This was observed in a 1990 study that evaluated cancer patients' interpretation of a hypothetical cancer therapy trial.[5] Of the 50 patients enrolled, 74% failed to acknowledge that both risks and benefits of trial participation were relevant. Furthermore, of the 30 (n = 50) subjects who agreed to enter the hypothetical trial, 33% focused entirely on the risks of this phase II study. Since then, other investigators have found variable levels of subject understanding. A study assessing brain tumor patients' understanding of a chemotherapy trial found that general trial comprehension was good, patients believed refusal to enroll would not impact treatment and that the decision to participate was voluntary; recall of risks, however, was low.[4] When 156 patients and 37 physicians involved in research projects at 4 Veterans Administration hospitals were interviewed, most patients knew they were research subjects, had voluntarily consented, and knew the details of their treatment, but few understood the research well.[8] Furthermore, readability analysis showed that the consent form language was at a college level of education.

The majority of the subjects in our series were said to have excellent or very good knowledge of the clinical trial in which they participated, but deficiencies were still observed. The specific concepts that proved difficult to grasp were not reported in our series, although other investigators have collected this information. Researchers using a validated measure of consent form quality found that many subjects were unaware of the unproved nature of a treatment, the lack of certainty about trial benefits, and the idea that an important aim was to benefit future patients.[1,4,11] This is an illustration of the therapeutic misconception, which is a failure to distinguish treatment from research evaluating the possible utility of an intervention. In other words, subjects often believe the physician is providing treatment known to be effective when, in fact, he or she is performing an intervention with the intent of learning whether or not it is actually therapeutic. Randomization is also difficult for many participants to understand, which may be a reflection of the therapeutic misconception as patients often feel that their doctor is acting in their best interests by choosing the best therapy for the individual patient. In a survey conducted on rheumatology research participants to determine their satisfaction with the process and ability to understand informed consent, most participants reported they were satisfied with the process and understood the trial concepts. However, the investigator states that trial concepts may be misunderstood regardless of self-assessment of understanding and suggests subjects may prefer to believe investigators know which treatment they are receiving and have made a good treatment decision specific to their case, despite having been told otherwise.[2]

Two aspects of compliance with consent procedures in our series could foster greater understanding of clinical trials methods, risks, and benefits. By having a copy of the signed consent form, subjects would be able to refer back to that document if questions arose. Similarly, by having study staff contact information, subjects would have a means of asking questions and obtaining clarification after the consent discussion had occurred and the form had been signed.

To our knowledge, this is the first report comparing demo-

Table 3. Descriptive Statistics by Gender, with Fisher's Exact Test *P*-values

	Male			Female			
	N	Mean/%	SD	N	Mean/%	SD	*P*-value
Age	**298**	**57.81**	**16.87**	**271**	**55.17**	**16.27**	**0.025**
Year of visit							**0.225**
2005	32	11.3		25	9.1		
2006	86	30.4		68	24.6		
2007	63	22.3		87	31.5		
2008	63	22.3		67	24.3		
2009	39	13.8		29	10.5		
Gender							**<0.001**
Male	242	81.2		180	66.4		
Female	56	18.8		91	33.6		
Knowledge of study							**0.350**
Excellent	101	34.5		94	34.9		
Very Good	134	45.7		130	48.3		
Partial	58	19.8		43	16.0		
None	0	0.0		2	0.7		
Consent							**0.217**
No	4	1.4		1	0.4		
Yes	288	98.69		265	99.6		
Contact information							**0.077**
No	6	2.0		1	0.4		
Yes	288	98.0		268	99.6		
Consent process was appropriate							**0.478**
Appropriate	294	100.0		268	99.6		
Inappropriate	0	0.0		1	0.4		
Satisfaction with CTRC							**0.214**
High	278	96.2		258	97.7		
Moderate	11	3.8		6	2.3		
Low	0	0.0		0	0.0		
Satisfaction with research staff							**0.824**
High	279	95.9		253	95.8		
Moderate	12	4.1		10	3.8		
Low	0	0.0		1	0.4		

Abbreviation: CTRC, Clinical and Translational Research Core

graphic features and specific clinical trial understanding of oncology patients to those without a cancer diagnosis. Patients with cancer were generally older than those enrolled in studies for other diagnoses, which is not surprising given that cancer tends to develop later in life. Oncology patients had inferior understanding of clinical cancer trials when compared to patients with other diagnoses. The reason for this is not clear. Oncology trials tend to be complicated in methods, potential side effects, and drug administration schedules, which could increase the likelihood that subjects might struggle to understand the information presented to them.

If informed consent standards are rigorous and understanding of the study itself is often inadequate, how can we help ensure that subjects comprehend as well as possible the methods, risks, benefits, and rights to choose or refuse participation? Other investigators have provided enhanced educational materials and modalities in hopes of optimizing this process. Specifically, a discussion with a research nurse via phone, face-to-face interviews, simplified consent forms, computer-based presentations, videotaped presentations, administering a quiz and then reviewing responses with participants, and utilization of the teach-back method in informed consent discussions (ie, asking the potential subject to summarize the key elements of the study in his/her own words) all have been tried with variable success.[12-14] Having a study staff member or educator spend additional time discussing a clinical trial with the subject appears to be slightly more effective than the other aforementioned options. Further research is needed to identify an efficient means of effectively increasing clinical research subjects' knowledge of the trials in which they participate, particularly for oncology patients and others receiving complex, high-level care.

There are limitations to our study. The questionnaire administered during subject interviews was not validated. Although the 2 advocates and the nurse manager conducting the interviews asked the same questions of each subject, interpretation of subjective questions—namely, those delving into level of understanding—probably varied between the 3 interviewers. Administration of study questions verbally also may have been a limitation in that subjects may not have openly provided feedback because of concerns that their response may affect the quality of their care. The medical and psychological status of subjects were not screened or evaluated, and these factors could affect participants' understanding of study aims, methods, and risks. Finally, specific concepts subjects found difficult to grasp, such as randomization and the goals of phase 1 trials, were not recorded. We therefore cannot comment on what aspects of clinical trials should be covered more thoroughly when educating participants.

CONCLUSION

In summary, our study shows excellent compliance with consent requirements by research teams on our clinical research unit. The level of subjects' knowledge of research is quite respectable, particularly among those participating in nononcology studies. The level of knowledge decreases in the subjects above age 60. The study documents the need for greater effort to inform oncology and older subjects about research protocols.

Table 4. Descriptive Statistics by Age Group, with Fisher's Exact Test *P*-values

	Ages 20-40 Years			Ages 41-60 Years			Ages 60 Years or Older			
	N	Mean/%	SD	N	Mean/%	SD	N	Mean/%	SD	*P*-value
Age	**95**	**26.23**	**7.26**	**200**	**53.24**	**5.11**	**275**	**69.47**	**6.33**	**NA**
Year of visit										**0.170**
2005	4	4.3		19	9.7		34	12.9		
2006	21	22.8		58	29.7		75	28.4		
2007	28	30.4		49	25.1		64	24.2		
2008	21	22.8		48	24.6		61	23.1		
2009	18	19.6		21	10.8		30	11.4		
Gender										**0.061**
Male	47	49.5		107	53.5		117	42.7		
Female	48	49.5		93	46.5		157	57.3		
Knowledge of study										**<0.001**
Excellent	40	42.6		79	40.3		76	27.8		
Very Good	47	50.0		94	48.0		123	45.1		
Partial	7	7.4		22	11.2		73	26.7		
None	0	0.0		1	0.5		1	0.4		
Consent										**0.225**
No	2	2.1		2	1.0		1	0.4		
Yes	93	97.9		193	99.0		268	99.6		
Contact information										**0.883**
No	1	1.1		3	1.5		3	1.1		
Yes	93	98.9		196	98.5		268	98.9		
Consent process was appropriate										**1.000**
Appropriate	94	100.00		199	100.00		270	99.6		
Inappropriate	0	0.0		0	0.0		1	0.4		
Satisfaction with CTRC										**0.798**
High	90	97.8		187	97.4		260	96.3		
Moderate	2	2.2		5	2.6		10	3.7		
Low	0	0.0		0	0.0		0	0.0		
Satisfaction with research staff										**0.569**
High	89	97.8		188	95.9		256	95.2		
Moderate	2	2.2		7	3.6		13	4.8		
Low	0	0.0		1	0.5		0	0.0		

Abbreviation: CTRC, Clinical and Translational Research Core

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An Exploratory Study of the Relation of Population Density and Agricultural Activity to Hematologic Malignancies in North Dakota

Patricia L. Watkins, MS; John M. Watkins, MD

ABSTRACT

Introduction: Established risk factors for hematologic cancers include exposure to ionizing radiation, organic solvents, and genetic mutation; however, the potential roles of environmental and sociological factors are not well explored. As North Dakota engages in significant agricultural activity, the present investigation seeks to determine whether an association exists between the incidence of hematologic cancers and either population density or agricultural occupation for residents of south central North Dakota.

Methods: The present study is a retrospective analysis. Cases of hematologic malignancies and associated pre-malignant conditions were collected from the regional Central North Dakota Cancer Registry, and analysis of study-specific demographic factors was performed.

Results: Significantly higher incidence of hematologic cancers and pre-malignant disorders was associated with residence in an "urban" county and rural city/town. Within the latter designation, there was a higher rate of self-reported agricultural occupation (40% vs 10%, $P < 0.0001$).

Conclusions: The increased incidence of hematologic cancer in low population density areas of south central North Dakota supports the need for more detailed prospective research centered on agricultural exposures.

INTRODUCTION

Hematologic malignancies include such diseases as acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelomatous disorders, and Hodgkin and non-Hodgkin lymphoma (NHL).[1-7]

Established risk factors for hematologic cancers include exposure to ionizing radiation;[8] however, potential roles of socioenvironmental factors are not well explored. Specific to agricultural exposure, several investigations have demonstrated associations more specific to pesticide use, including its handling,[9] chemical type,[10,11] and timing of exposure with respect to childbirth.[12,13]

As a formal descriptive study of potentially associated sociodemographic factors specific to North Dakota has yet to be performed, the present study seeks to determine whether a correlation exists between hematologic malignancies and agricultural activity in North Dakota. It is hypothesized that increased exposure to agricultural activities in North Dakota will be associated with an increased incidence of hematologic malignancies and associated premalignant conditions (such as myelodysplastic syndrome [MDS]). Findings consistent with this hypothesis would support larger research efforts aimed at delineating specific hazards associated with agriculture in North Dakota that may increase risk of hematologic cancers.

METHODS

The present study was a retrospective review of medical records designed to examine differences in incidence of hematologic cancers between rural and urban regions of North Dakota. Following approval by the Institutional Review Boards (IRBs) at the University of North Dakota School of Medicine (Grand Forks, ND) and the 2 participating institutions (St Alexius Hospital and MedCenter One, Bismarck, ND), a research database was created.

Eligible cases were identified by query of the Central North Dakota Cancer Registry. Inclusion criteria were clinically defined hematologic malignancy or MDS diagnosed between 2002 and 2010, age > 18 at diagnosis, and residence in the following North

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Author Affiliations: University of North Dakota, School of Medicine and Health Sciences, Southwest Campus–Bismarck; c/o Bismarck Cancer Center, Bismarck, ND.

Corresponding Author: John M. Watkins, MD, Bismarck Cancer Center, 500 N 8th St, Bismarck, ND 58501; phone 701.222.6100; fax 701.222.6150; e-mail john.m.watkins.md@hotmail.com.

Dakota counties: Burleigh, Morton, Grant, Hettinger, Stark, or Emmons (selected due to dominance of the adult hematology/oncology practices of the participating institutions and thus anticipated near-complete capture and retention of patients diagnosed within the region).

Study Objectives

The principal objective of this investigation is to determine whether an association exists between incidence of hematologic malignancies and agricultural activity for residents of south central North Dakota, employing available population and demographic data.

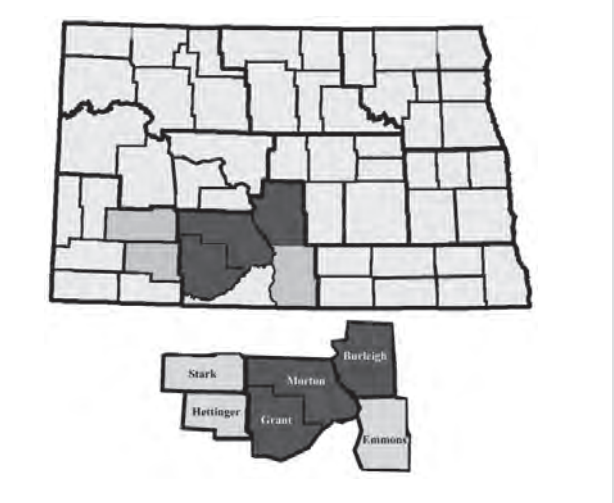
Population Stratification

In order to assess frequency of hematologic cancers by level of agricultural activity, several stratifications were employed. First, individuals were classified by the county of residence at diagnosis, stratified into "urban" and "rural" agricultural activity levels. Counties were designated as "urban" if < 50% of acreage was devoted to cropland, and "rural" if > 50%. Data on percentage of acreage devoted to cropland was obtained from publicly available data at the United States Department of Agriculture, National Agricultural Statistics Service database.[14] Classification of counties is demonstrated in Figure 1. A second measure was population density, stratified into high vs low and classified based upon city/town of residence at the time of diagnosis. Cities were categorized as high population density if the city contained above the 25th percentile of total state residents in the 2000 census, and low if below the 25th percentile. These data were acquired from the North Dakota State Data Center database.[15] Third, patients' charts were reviewed to determine whether documented occupation in agriculture (eg, any farming activity) was noted at or prior to the time of diagnosis.

Statistical Analysis

All statistical analyses were performed using SPSS Version 10 (SPSS, Inc.; Chicago, Illinois). Frequencies and relative percentages were computed for demographic and clinical characteristics of patients. The Mann-Whitney U test was employed to assess differences between comparison populations in age at presentation, smoking status, or percent of individuals reporting agricultural work. Missing data were excluded from analysis. Incidence of hematologic disorders was recorded as a number per thousand derived from the group incidence divided by the population of represented cities, as obtained from the North Dakota State Data Center database.[15] Chi-Square test was performed to test for differences in hematologic cancer incidence between rural and urban as well as high and low population densities. An alpha level of .05 was employed for this study, with statistical significance accepted where *P*-value was < .05.

Figure 1. Map of North Dakota, with Included Regions Highlighted



Classification of agricultural activity: dark gray = urban; medium gray = rural.

Table 1. Study Population Characteristics

Characteristic	Study Population[a] n (%)
Age at diagnosis	
Median	70
(range)	(19 - 89)
Gender	
Male	321 (53)
Female	286 (47)
Smoking history	
Yes	271 (44)
No	278 (45)
Not recorded	64 (11)
Agriculture occupation	
Yes	92 (15)
Hematologic disease	
Acute lymphoblastic leukemia	8 (1)
Acute myelogenous leukemia	58 (9)
Chronic lymphocytic leukemia	85 (14)
Chronic myelogenous leukemia	23 (4)
Hairy cell leukemia	8 (1)
Multiple myeloma	52 (8)
Plasmacytoma	7 (1)
Myelodysplastic syndrome	118 (19)
non-Hodgkin lymphoma	231 (38)
Hodgkin lymphoma	23 (4)

[a]Missing data was excluded from analysis; 6 patients without gender, 64 patients without smoking history, and 108 patients without occupation data.

RESULTS

Patient Characteristics

Between 2002 and 2010, 613 patients were identified for inclusion in this study. Patient and disease data are shown in Table 1. A comparison of patient factors by county

Table 2. Population Characteristics by Agricultural Activity

	Low n = 496 (%)	High n = 117 (%)	*P*-value
Age			
Median	72	68	0.171
Gender			
Male	262 (54)	59 (50)	0.554
Female	228 (46)	58 (50)	
Smoking history			
Yes	220 (49)	51 (50)	0.801
No	228 (51)	50 (50)	
Agriculture occupation			
Yes	63 (16)	22 (21)	0.201

Table 3. Population Characteristics by Population Density

	High n = 484 (%)	Low n = 129 (%)	*P*-value
Age			
Median	70	71	0.443
Gender			
Male	247 (52)	74 (57)	0.251
Female	231 (48)	55 (43)	
Smoking history			
Yes	214 (49)	57 (50)	0.797
No	222 (51)	56 (50)	
Agriculture occupation	42 (10)	44 (40)	**<0.0001[a]**

[a]Statistically significant with an alpha level of 0.05.

cropland ("urban/rural") classification is demonstrated in Table 2, and city/town high vs low population density in Table 3.

Urban vs Rural

Residence in an urban county (< 50% cropland) was associated with a significantly higher incidence of hematologic cancers and pre-malignant disorders as compared to rural (6.4 per 1000 vs 4.6 per 1000, $P = .0027$). When MDS was excluded, the difference was no longer statistically significant (5.0 per 1000 vs 4.0 per 1000, $P = .0576$).

High vs Low Population Density

The low population density group had a significantly higher incidence of hematologic cancers and premalignant disorders as compared to the high population density group (7.9 per 1000 vs 5.5 per 1000, $P = .0002$). When MDS was excluded, the difference remained statistically significant (6.7 per 1000 vs 4.4 per 1000, $P = .0001$).

DISCUSSION

Increased risk of hematologic malignancies for agricultural workers has been reported previously in several states with significant agricultural activity.[9-13,16] The present study suggests a similar increase in risk for agricultural workers in North Dakota. Patients residing in low population density areas, where a significantly higher number of patients self-reported an agricultural occupation, were found to have a significantly higher incidence of hematologic disorders. While the results obtained in high vs low population density groups supported the study hypothesis, the expected pattern of incidence was not observed in urban vs rural groups; indeed, the urban group had significantly higher incidence of hematologic malignancies.

Several possibilities exist for these findings. First, the definition of urban residence was determined at the county level, which was likely insufficiently sensitive to properly measure the effects of local agricultural activity to which the individual patient would have been exposed. This is substantiated by the subsequent study findings of increased malignancy risk with lower population density; thus, residence in lower population density areas of these "urban" counties increases risk. Whether this is due to differences in agricultural practices (eg, intensity of pesticide use) cannot be determined from the available data; however, it is noteworthy that there was no significant difference in agricultural occupation between the urban/rural designations. Second, an alternative characterization of urban vs rural (presently dichotomized to above/below 50% cropland) could be entertained.

As with all epidemiologic studies, the present investigation is limited by its retrospective nature. Agricultural occupation data was gleaned from social history information recorded by the physicians caring for each patient, and subsequently imported into the registry database. As such, level of occupational data available was insufficiently detailed, and no specific information on toxin exposure was recorded (eg, type, duration, age at exposure). Furthermore, patients residing in areas of agricultural activity, but whose work is not specifically agricultural, would be expected to have at least some exposure in common with agricultural workers. The low population density demographic would capture this, but data quantifying risk factors has not yet been prospectively collected. Additionally, the retrospective nature of this study limited the inclusion of factors measuring the duration of work in agriculture or residence in a specific location. Available records indicated only occupation and location of residence at the time of diagnosis.

Based upon the present study demonstrating an association between low population density and risk hematologic cancers, and increased probability of agricultural occupation in low population density areas the next steps of this investigation would be to prospectively evaluate occupational exposures and associated risk of hematologic cancer. As prior investigations have associated pesticides with risk of NHL,[9-11] and specified that length[9] and intensity of exposure[12] correlate with risk, recording the types of pesticides used, length of exposure to each pesticide, and han-

dling practices during exposure would allow for more accurate examination of risk within our population.

The ability to generalize the results of this study may be limited by the nature of the population characteristics. First, as stated previously, the variability of pesticide type and level of exposure by region and crop could not be determined from the present study. As some pesticides have a stronger association with hematologic cancers than others,[9] the results of the present study would be applicable only to regions with similar crop and pesticide use profiles. Second, North Dakota is relatively homogeneous with respect to ethnoracial heritage (predominantly northern/western European white), thus the results may not be generalizable to other agricultural workers.

The present study found a significantly higher incidence of hematologic cancers and premalignant conditions in low population density regions of North Dakota, which suggests that further investigation into specific agricultural activities (including pesticide agents used and exposure) is warranted.

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A Case Report of Meningococcal Disease in a Neonate

Sanket Shah, MD; Jody R. Gross, MD; C. Todd Stewart, MD

ABSTRACT

Neonatal meningococcal meningitis (NMM) is rare, although early onset and late onset forms of meningococcal sepsis in neonates have been reported. The outcome of meningococcal disease can be fatal and depends on the innate immune system, age, serogroups, pre-existing antibodies, and other unknown host factors. The presentation of NMM differs from that in children and adolescents and may present with fever, poor feeding, decreased activity, seizures, altered consciousness, respiratory distress, or rash. Prompt identification and initiation of antibiotics is critical to survival. In the literature, very few cases of neonatal meningococcal disease have been reported in the United States. The average annual incidence of meningococcal meningitis in neonates is very low compared to the incidence of group B streptococcal meningitis. We present the youngest documented case (to the best of our knowledge) of neonatal meningococcal meningitis in the United States. We also present a review of the existing literature.

INTRODUCTION

Meningococcal meningitis is a rare infection in the first 4 weeks of life. The causative agent is *Neisseria meningitidis*, an encapsulated gram-negative, aerobic, intracellular diplococcus. The spectrum of disease ranges from mild fever to fulminant septic shock, purpura fulminans, coma, and death.

In 1916, Koplik reported the first case of neonatal meningococcal meningitis (NMM) in a 3-day-old infant born after a prolonged labor. The baby survived, but later developed hydrocephalus.[1] There have been 48 cases of NMM described since 1916. The incidence of NMM ranges from 0.8 to 1.3 per 100,000 in the US population.[2] We present what is, to the best of our knowledge, the youngest documented case of NMM in the United States. This patient presented with fever and rash, progressed rapidly to purpura, uncompensated septic shock, multiple organ dysfunction syndrome (MODS), and died within 12 hours of presentation.

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Author Affiliations: Marshfield Clinic, Marshfield, Wis: Department of Pediatrics (Shah); Department of Neonatology (Gross); Department of Pediatric Intensivists (Stewart).

Corresponding Author: Sanket Shah, MD, Neonatal-Perinatal Medicine Fellow, University of Tennessee Health Science Center Department of Pediatrics, Memphis, TN; e-mail sshah14@uthsc.edu.

CME available. See page 31 for more information.

CASE PRESENTATION

A 40-week gestation male, with a birth weight of 3425 grams, was born in a referral hospital by normal spontaneous vaginal vertex delivery to a 24-year-old woman with 2 previous pregnancies resulting in 1 miscarriage and 1 live birth; this was her third pregnancy. Her prenatal screening tests (including gonorrhea, chlamydia, syphilis, rubella, group B streptococcus, and complete blood count) were unremarkable. Her labor was normal and uncomplicated, lasting 16 hours. She received 1 dose of intravenous ceftriaxone during her postpartum stay for fever. The infant's Apgar scores were 7 and 8 at delivery, and he was discharged to home within 24 hours of birth.

The infant's newborn genetic screen was normal. He had a normal well-child examination 4 days after discharge. His 11-month-old brother had left foot cellulitis and cold symptoms that were being treated with cephalexin at the time of this infant's illness. Three days before onset of symptoms, the patient was taken to church for 2 hours, and several individuals held him, though none was reported as having been ill.

The patient's mother called the nurse line, reporting a fever of 103.2°F, irritability, rash, poor feeding, moaning and crying for the past 2 hours. The mother reported that the infant had been doing well until that morning, when he would cry at feeding attempts. She described the rash as localized to the abdomen, with variably sized pink to dark pink spots. No respiratory problems were reported. She was advised by the nurse to take the infant to the nearest emergency department (ED).

The mother presented to the ED with the 12-day-old infant

within an hour of her call to the nurse line. The infant had a temperature of 101.8°F, and the rash had spread to his extremities, with petechial lesions in the groin that were purplish to black in color. He looked visibly ill, appearing ashen and sleepy with some grunting. On physical examination, his anterior fontanel was soft and open, but sunken, and his eyes appeared sunken. His lungs were clear without wheezes or rhonchi. His response to painful stimuli was decreased. He was given acetaminophen that reduced his fever to 99°F. A complete blood count showed a white blood cell (WBC) count of 3500/uL, with 55% lymphocytes, 14% bands, 26% segmented neutrophils, and clumped platelets. Erythrocyte sedimentation rate, C-reactive protein, and electrolytes were normal. A chest radiograph revealed no acute pulmonary process and a normal cardiothymic silhouette. Blood and urine cultures were obtained, both of which eventually returned with no growth.

On admission to the pediatric floor, the infant looked visibly ill, was described as limp and hypotonic with prolonged capillary refill time, and petechiae and purpuric lesions covering his body. Ampicillin (200 mg/kg/day), gentamicin (5 mg/kg/day), and acyclovir (60 mg/kg/day) were given after lumbar puncture, within one hour of admission. He received a 30 cc normal saline bolus to treat hypotension (blood pressure 50/35 mmHg) and was transferred to the pediatric intensive care unit (PICU) due to his critical condition. An infectious disease specialist was consulted, and the antibiotic regimen was changed to ceftriaxone and linezolid. Because of respiratory failure, he was intubated 3 hours after arrival in the PICU. He continued to deteriorate, and the first cardiac arrest occurred 4 hours after PICU admission.

Laboratory results revealed disseminated intravascular coagulation (DIC) with D-dimer 5.00 µg/dL, fibrinogen 40 mg/dL, platelets 41000/ml, and INR 9.3 and severe metabolic acidosis with lactate >15 mmoL/L and potassium 7.4 mmoL/L. Cerebral spinal fluid (CSF) examination showed 3 WBCs/uL, 16 red blood cells/uL, total protein 76 mg/dL, and glucose 44 mg/dL. Initial gram stain of the CSF showed few neutrophils and no microorganisms, but it subsequently grew *N meningitidis*, serotype *B. Herpes* and enteroviral polymerase chain reaction (PCR) tests were negative. The PCR test from a nasopharyngeal swab was negative for respiratory syncytial virus and influenza A and B. Subsequent blood and viral cultures were negative. Despite multiple boluses of saline, fresh frozen plasma, and infusions of dopamine, norepinephrine, and epinephrine, the infant died 12 hours after his mother's phone call to the nurse advisor and 9 hours after hospital admission.

DISCUSSION

Although the incidence of meningococcal infection is relatively high in the first 2 years of life compared with other age ranges, the incidence in the first month of life is very low. From 1990 to 2002, there were 3335 deaths due to meningococcal disease reported in the United States, with the highest disease mortality rate reported in patients under 2 years of age.[3] In the pre-antibiotic era, there were 11 cases of meningitis reported, with treatment consisting of anti-meningococcal serum given intravenously or intrathecally.[4] With the use of antibiotics, the rate of complications has decreased to 16%. In 2003, a report[5] of population-based surveillance data in the United States from 1990 to 1999 found a higher incidence rate of neonatal meningococcal disease than previously estimated, but a rate similar to that found in patients aged 6 to 23 months.

Since the advent of antibiotics, only 37 neonatal cases have been reported in the English language literature,[1,4-9] with 18 of those reported in the United States; of these, 6 patients died due to either meningitis or uncompensated septic shock. One patient was a pregnant woman who was known to have meningitis before delivery. Her affected newborn developed petechial rash, uncompensated septic shock, and MODS, and the baby subsequently died.[10]

Based on these reports, the case fatality rate is at least 50% in those who presented with severe purpura, MODS, and/or DIC. While the complication rate may be decreased with the use of antibiotics, the incidence of meningococcal infection has not changed.

The clinical spectrum and organisms that cause neonatal meningitis differ in infants from older children and adults. *Neisseria meningitidis*, a gram negative, encapsulated, intracellular diplococcus, is the causative organism for meningococcal meningitis. The serotypes responsible for neonatal meningitis may be B, C, Y as well as nongroupable serotypes. There are so few cases that virulence patterns are impossible to determine; however, serotype B was found to be the most common cause of meningitis in all age groups.[11] While *N meningitidis* commonly causes sepsis and meningitis in children and adolescents, it rarely is associated with invasive infection in neonates. Leading causes of neonatal bacteremia, septicemia, and meningitis are group B streptococci, *Escherichia coli*, and *Listeria monocytogenes*. These pathogens commonly colonize the maternal rectovaginal area, and are thus most commonly associated with neonatal infection. Although *N meningitidis* may also colonize the female genital tract, it does so with much less frequency, and is therefore less often a cause for neonatal disease.[2,11]

The two most common forms of meningococcal disease are meningitis and meningococcemia. The time from onset of fever until death in severe meningococcemia is often as short as 12 hours.[8] Meningitis may initially present with fever, irritability, poor feeding, or poor activity with or without meningeal signs. Although the maculopapular rash is the distinctive sign of menin-

gococcal infection, it is seen in only 7% of cases.[4] The rash may rapidly evolve into prominent petechiae and purpura and may progress to purpura fulminans, a necrosis of the skin and underlying tissues due to thrombosis. Meningococcemia is a fulminant form of sepsis typified by severe septic shock, acidosis, DIC, and MODS. Despite rapid diagnostic testing, antibiotic treatment, and general support care in the PICU, mortality rates remain high. Patients with purpura fulminans, shock, acidosis, hyperpyrexia, DIC, and positive blood culture have a very poor prognosis, and most deaths occur within 24 to 48 hours of hospitalization.[4] Meningitis can be complicated by empyema, cerebral abscess, obstructive hydrocephalus, and ventriculitis. The most common neurological sequela is deafness.

Diagnosis is made by isolation of *N meningitidis* from normally sterile body fluids.[4] Spinal fluid cultures may be positive without pleocytosis, as described in our patient.[12] Patients with CNS infection without CSF pleocytosis are at significantly higher risk of adverse outcomes such as death and limb loss than meningococcal bacteremia alone.[14] Absence of CSF pleocytosis can be considered as a prognostic factor.[14] Penicillin G or cefotaxime remain the initial drugs of choice.[13] Duration of therapy depends on the patient's clinical response, but a minimum of 10 days is indicated for a neonate. Before discharge, a brain sonogram should be done to assess for encephalomalacia, since neonatal meningitis can have profound implications for an infant's neurodevelopment. Frequent sequelae include deafness, hydrocephalus, seizure disorders, speech disorders, and mental and motor disabilities. Because of the low incidence of this particular organism, it is difficult to specifically determine if there is more or less propensity for producing each of the common sequelae; however, neonatal meningitis in and of itself is a risk for poor outcome.[11] Significant sequelae develop in up to 60% of surviving infants. In order to prognosticate, it is vital that a repeat LP be done at the end of therapy to demonstrate that the CSF is indeed sterile, and that imaging be done for the presence or absence of abscesses and/or thrombosis. The patient should be followed for long-term complications with developmental, neurologic, and hearing evaluations.

CONCLUSION

Meningococcal infection should be considered in the differential diagnosis of rash in the neonate, especially when rash is accompanied by other signs of illness such as fever, poor appetite, and abnormal appearance. Progression of the disease is more rapid than in other types of meningitis, and the first 24 to 48 hours are critical.

Rapid recognition of meningococcal infection, along with antibiotic treatment and supportive care, remain keys to successful treatment of invasive meningococcal infection. In most patients, the first sign of illness is fever that can be followed by decreased appetite, nausea, and vomiting. However, some investigations have found that the first signs of sepsis are fever, abnormal skin color, cold hands and feet, leg pain, and thirst (in patients old enough to describe this).

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CME

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Quiz: A Case Report of Meningococcal Disease in a Neonate

EDUCATIONAL OBJECTIVES

Participants in this CME should be able:

1. To recognize the various presenting symptoms and signs of meningococcal disease in the neonate.
2. To understand the appropriate evaluation and treatment of this disorder.
3. To understand the mortality rates and sequelae of this disorder.

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QUESTIONS

1. While *Neisseria meningitidis* is a frequent cause of sepsis and meningitis in children and adolescents, it rarely is associated with invasive infections in neonates.
   - ❑ True
   - ❑ False
2. The incidence of meningococcal infection in the first 2 years of life is relatively low but carries a higher mortality rate.
   - ❑ True
   - ❑ False
3. *Neisseria meningitidis* is an encapsulated gram negative, aerobic, intracellular diplococcus.
   - ❑ True
   - ❑ False

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You may earn CME credit by reading the designated article in this issue and successfully completing the quiz (75% correct). Return completed quiz to *WMJ* CME, 330 E Lakeside St, Madison, WI 53715 or fax to 608.442.3802. You must include your name, address, telephone number, and e-mail address.

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4. The clinical spectrum of meningitis due to meningococcal disease in the neonate differs from that in older children and adolescents and may present with only fever and poor feeding or decreased activity without meningeal signs.
   - ❑ True
   - ❑ False
5. Neonates without cerebral spinal fluid (CSF) pleocytosis may still have meningococcal meningitis, and this is a negative prognostic sign.
   - ❑ True
   - ❑ False
6. A maculopapular rash is a distinctive sign of meningococcal infection and is seen in the majority of cases.
   - ❑ True
   - ❑ False
7. If an infant survives meningococcal meningitis, the incidence of significant sequelae is relatively low.
   - ❑ True
   - ❑ False
8. Complications of meningococcal meningitis include empyema, cerebral abscess, and obstructive hydrocephalus.
   - ❑ True
   - ❑ False
9. The case fatality rate of neonatal meningococcal disease for those infants who present with severe purpura and multisystem organ failure is at least 50%.
   - ❑ True
   - ❑ False
10. The leading causes of neonatal bacteremia, septicemia, and meningitis are:
    a. *Neisseria meningitidis*
    b. Group B streptococci
    c. *Listeria monocytogenes*
    d. *Escherichia coli*
    e. *Staphylococcus* species
    - ❑ All of the above
    - ❑ A, B, C, and D
    - ❑ A, C, and C
    - ❑ B, C, and D
    - ❑ A, B, and E

Combined Rectovesicular Injuries from Low Velocity Penetrating Trauma in an Adult

SreyRam Kuy, MD, MHS; Panna A. Codner, MD, FACS; Michael Guralnick, MD, FRCSC; Anahita Dua, MD; Jasmeet Paul, MD

ABSTRACT

The most common concomitant site of injury following a penetrating anorectal injury is the genitourinary tract. In anorectal penetrating injuries, other organ injuries must be thoroughly evaluated. In the presence of concomitant rectal and posterior bladder injury, consideration should be given to omental interposition between the surgically repaired organs to prevent fistula formation. Fecal diversion may be required depending upon the integrity of the anal sphincters. Combined rectal and genitourinary trauma from stab wounds or impalement is rare, and requires an interdisciplinary approach utilizing the collaborative expertise of both trauma surgical and urology teams to optimize the intraoperative and postoperative care of the patient.

CASE REPORT

A 41-year-old man with a history of depression was brought to the emergency department after multiple self-inflicted transanal stab wounds with a 6-inch steak knife. There was also an incidental stab wound involving the left wrist. The knife was removed by the patient prior to presentation. On physical exam he had diffuse abdominal pain, but was otherwise hemodynamically stable. Digital rectal exam revealed gross blood and inability to squeeze on the examining finger consistent with sphincter muscle injury. A Foley catheter revealed gross hematuria. The patient was taken to the operating room for proctoscopy, cystoscopy, and exploratory laparotomy. Intraoperative findings on proctoscopy included 3 rectal lacerations involving the internal and external anal sphincters. The largest laceration measured 3 cm in length and was located 5 cm from the anal verge at the 12 o'clock position. The trajectory of this wound was directed into the posterior prostatic urethra and posterior bladder neck. The Foley catheter was easily palpated through this injury. The rectal injury was repaired transanally with a single-layer, running, locking 3-0 chromic stitch. The 2 additional lacerations at the 3 o'clock and 6 o'clock position were repaired in a similar fashion.

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Author Affiliations: Department of Surgery, Medical College of Wisconsin, Milwaukee, Wis (Kuy, Codner, Dua, Paul); Department of Urology, Medical College of Wisconsin, Milwaukee, Wis (Guralnick).

Corresponding Author: SreyRam Kuy, MD, MHS, Department of Surgery, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226; phone 210.535.2877; fax 414.805.8641; e-mail srkuy@mcw.edu.

Cystoscopy demonstrated a laceration to the posterior bladder neck in the midline communicating with a large laceration in the left posterolateral prostatic urethra. The laceration was deep such that peri-prostatic fat was grossly visualized. At laparotomy there was no evidence of intraperitoneal bladder injury or other bowel injuries. The bladder neck laceration was repaired through a midline cystotomy using a running 3-0 Vicryl stitch (Figure 1). A vascularized omental flap was dissected and placed between the 2 repairs of bladder and rectum to minimize fistula formation. Ureteral stents, a suprapubic catheter, and urethral Foley catheter also were placed. The extensive damage to the anal sphincter mechanism required a diverting loop sigmoid colostomy with presacral drain placement. Other minor injuries were lacerations to both hands, which were sutured by plastic surgeons.

The patient's hospital course was unremarkable, and on postoperative day (POD) 9 he was discharged to a psychiatric facility. On follow-up (POD 22) a retrograde urethrogram suggested continued prostatic urethral extravasation and the Foley catheter was left in place. A subsequent urethrogram 3 weeks later showed no evidence of extravasation or rectourethral fistula, and both catheters were removed. The ureteral stents were removed endoscopically a week later. Five months later the patient underwent reversal of the colostomy. He is now 8 months out from his injury with normal voiding, no incontinence, and no evidence of fistula formation.

DISCUSSION

Genitourinary trauma is uncommon, with the majority of injuries being extraperitoneal bladder trauma (70%-95%) associated with pelvic fractures.[1] There is a higher reported incidence of genitourinary injury and combined genitourinary-rectal injuries with high velocity penetrating trauma. In a report of all penetrating rectal trauma at a single institution over a 13-year period[2] there were 200 cases of penetrating rectal injury, with 17 cases (8.5%) of concomitant genitourinary injuries (13 bladder injuries, 3 urethral injuries, and 1 ureteral injury), all associated with

gunshot wounds. Complications in 17 patients with combined penetrating rectal and genitourinary injuries revealed abscesses (pelvic, suprapubic, and subphrenic) in 18%, bladder stones in 12%, and urethral strictures in 12%. A case series of 69 gunshot wound patients treated at a single academic institution over a 9-year period[3] compared the management and postoperative complications of these high velocity penetrating injuries. The review identified 29 patients with isolated rectal injuries, 16 with isolated bladder injuries, and 24 with combined rectal and bladder injuries. There were 2 cases complicated by colovesical fistula formation and 2 cases of urinoma formation, all of which occurred only in those patients with combined rectal and posterior bladder injuries. Because of the higher incidence of postoperative complications (fistula, urinoma, abscess) in the combined rectal and genitourinary injuries, the authors of both studies suggested that these cases may benefit from placement of an omental interposition flap between the rectal and bladder repairs. Though both of these case series reviewed gunshot injuries, not low velocity injuries such as impalement or stab wounds as occurred in our patient, they offer insight into the complications that occur following combined rectal and bladder injuries. Because of concerns about possible fistula formation, we chose to interpose omentum between the rectal and bladder neck repairs.

The need for fecal diversion in the management of penetrating rectal injuries is debatable. A study reported in 2006 examined the management of nondestructive (all less than 25% circumferential injury) penetrating extraperitoneal rectal injuries without fecal diversion.[4] These were diagnosed on proctoscopy, and any intraperitoneal injury was repaired primarily while extraperitoneal injuries were left to heal secondarily. No presacral drainage was used. When comparing 14 patients managed in this fashion to historical matched controls that were treated with fecal diversion (loop colostomy or Hartmann's procedure), the researchers noted a shortened hospital stay in the nondiverted group (7.2 vs 9.8 days) that was not statistically significant, and no occurrences of retroperitoneal abscesses in either group. This study suggests that nondestructive penetrating rectal injuries could be managed successfully without fecal diversion. However, it is important to note that in our case the patient did not have a typical nondestructive penetrating rectal injury. Instead, lacerations to both the internal and external anal sphincters in multiple locations exceeding 25% of the anal circumference were identified. Additionally, there was a bladder neck injury with a full-length prostatic urethral laceration, which we felt altered our treatment algorithm to include fecal diversion for maximum healing.

Rare penetrating urethral injuries (anterior and posterior) are typically treated by primary repair with urinary diversion.[5] More common is traumatic disruption of the posterior urethra, which is usually associated with pelvic fracture. These types of injury are generally managed with initial suprapubic catheterization for urinary diversion and delayed urethroplasty.[6] In the case of bladder neck laceration, repair is indicated in order to preserve urinary continence (due to damage to the external sphincter by the urethral disruption). With rectal injury, surgical repair is indicated to prevent infection of the associated pelvic hematoma as well as fistula formation. In our case, while the urethra was not completely disrupted, there was a full thickness laceration of the bladder neck (ie, internal urinary sphincter) extending toward the prostatic apex and external urinary sphincter. Thus there was a concern about future incontinence due to possible compromise of both urinary sphincters. Surgically, the bladder neck was the only accessible defect. Therefore, we felt it was important to repair it primarily to preserve the integrity of the internal sphincter.

Figure 1. Laceration of the Posterior Wall of the Bladder Neck Seen through a Midline Cystotomy.

Whether suprapubic catheter drainage is needed in addition to urethral catheter drainage is also debatable. One study[3] showed a higher rate of suprapubic catheter drainage in the combined rectal and bladder injury group (88%) compared with the isolated bladder injury group (56%), but there was no reduction in fistula/urinoma formation with suprapubic catheter drainage, leading the authors to conclude that suprapubic catheter drainage of bladder injuries should be reserved for cases in which long-term catheterization is anticipated or the repair is extensive or incomplete. In our case, with an injury extending from the bladder neck to the prostatic apex in which we could only repair the bladder neck, we chose to use both suprapubic and urethral catheters in an effort to maximize drainage. However, it is possible that a urethral catheter alone would have sufficed.

CONCLUSION

In anorectal penetrating injuries, other organ injuries must be ruled out. The most common concomitant site of injury following a penetrating anorectal injury is the genitourinary tract, and a high index of suspicion must be maintained. In the presence of concomitant rectal and posterior bladder injury, consideration

should be given to omental interposition between the surgically repaired organs to prevent fistula formation. Fecal diversion may or may not be used in addition. Importantly, an interdisciplinary approach utilizing the collaborative expertise of both trauma surgical and urology teams optimizes the intraoperative and postoperative care of the patient.

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Medical College of Wisconsin Researchers Tackle Concussions From All Angles

Joseph E. Kerschner, MD

The national dialogue on traumatic brain injury has reached significant amplitude with the public platform of professional sports raising awareness, the experiences of soldiers over a decade of war reinforcing the implications, and the medical community rising with innovative efforts to improve diagnosis and care.

Of the estimated 3.8 million traumatic brain injuries (TBI) sustained each year in the United States, more than 75% are considered concussions, frequently termed mild TBI. Increasingly common among adult and youth athletes in impact sports, concussion also is recognized as an all-too-frequent, combat-associated wound of the conflicts in the Middle East. Combined with civilian risk from unintentional and intentional injury, concussions are a serious public health problem.

Acute symptoms manifest as a disturbance in cognition, and individuals can experience post-concussion syndrome, of which headaches and protracted symptoms are characteristic. Over the long term, concussions can yield even more devastating health concerns, including depression, cognitive impairment, dementia, and chronic traumatic encephalopathy.

As the nature of the injury suggests and the variety of projects at the Medical College of Wisconsin (MCW) demonstrates, better understanding of mild TBI requires a multidisciplinary approach. Concussion research led by MCW faculty includes expertise in neurosurgery, neurology, pediatrics, orthopaedic surgery, psychiatry and behavioral medicine, physical medicine and rehabilitation, emergency medicine, and primary care.

We are learning that how a concussion is sustained may affect its health consequences. Neurosurgery researchers Frank A. Pintar, PhD, and Brian Stemper, PhD, are funded by the Veterans Administration to study the differences in outcomes in concussions caused by blunt trauma, common in automobile collisions, versus those that are blast-induced, which have multiplied dramatically for military troops with the proliferation of improvised explosive devices.

The team is utilizing a rat model of injury, and their research suggests that although blast TBI and blunt TBI have similar acute outcomes, their chronic outcomes may be different. The researchers will conduct post-injury assessments of amnesia, spatial learning deficits, neuromotor deficits, anxiety-related behavior and aggression, adhedonic behavior, brain edema, and brain tissue pathology over a 4-year period. It is anticipated that better understanding the pathophysiology of these causative mechanisms will influence treatment and rehabilitation methodology.

Neuropsychologist Michael McCrea, PhD, is leading an additional area of innovative research in mild TBI as his team aims to determine which of four common screening tools is the most valid and reliable for assessing concussion and recovery. Dr McCrea is a member of the NFL Head, Neck and Spine Committee, and was part of the Concussion in Sports Group responsible for the 2008 Zurich international consensus statement on concussion in sport that led to new standards in sports-related concussion management.

Funded by a US Department of Defense grant, Dr McCrea's team intends to collect baseline tests on 2,100 Milwaukee area high school and college athletes. If and when any of these athletes sustains a concussion, the research

> Assessing recovery is critical for making return-to-play decisions following sports-related concussion, and the stakes are even higher in the still-developing brains of children and adolescents.

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Dr Kerschner is dean of the medical school and executive vice president of the Medical College of Wisconsin.

team performs an immediate assessment plus several follow-up exams, enabling comparison of the 4 tests. The goal is to identify the optimal tool for measuring the injury's effect and for guiding clinical decisions about a patient's readiness to return to activity. While benefiting the public good, the results will hopefully transfer to military applications as well, helping determine a soldier's fitness to return to duty.

Assessing recovery is critical for making return-to-play decisions following sports-related concussion, and the stakes are even higher in the still-developing brains of children and adolescents. Neuropsychologist Thomas A. Hammeke, PhD, is using functional imaging to better understand functional abnormalities and recovery mechanisms associated with the acute and subacute stages of concussions in high school athletes.

His team's recent study revealed changes in brain activation patterns that correlate strongly with changes in self-reported post-concussive symptoms and neurocognitive performance. This was marked by underactivation in the right hemisphere attentional networks within 24 hours of injury, followed by hyperactivation 7 weeks after injury, suggesting neurocognitive functions can recover enough for an individual to achieve normal performance with compensatory cognitive operations. As such, functional MRI may be an accurate imaging biomarker for documenting the transition from acute to subacute stages of recovery and for assessing the efficacy of interventions.

Interventions for concussion may be as straightforward as inactivity. Pediatric emergency medicine physician Danny Thomas, MD, along with Dr Hammeke and neuropsychologist Jennifer Apps, PhD, recently finished enrolling patients in a study funded by the MCW Injury Research Center examining the effect of rest on recovery from pediatric concussion. It will compare 5 days of strict rest to the current standard of care, which is a slow return to school and activity. Results are expected this summer.

As research begins to answer our many questions about concussions, we are able to create and update clinical guidelines and policy to more effectively treat and limit injury. In 2012, pediatric primary care sports medicine specialist Kevin Walter, MD, with Dr Apps, published the first book of its kind to summarize research and provide guidelines for understanding diagnosis, management and outcomes of concussions in children and adolescents.

Dr Walter's expertise on the topic is well-known around the state, where he is a vigorous advocate for young athletes. As a member of the Wisconsin Interscholastic Activities Association's (WIAA) Sports Medicine Advisory Committee, Dr Walter worked closely with peers, legislators, community leaders and the WIAA to craft legislation mandating that players age 19 and younger who suffer a possible concussion are not allowed to return to play until they are cleared by a health care professional trained in concussion evaluation and management. The "Sidelined for Safety Act" was signed into Wisconsin law on April 2, 2012.

Dr Walter—who was just appointed to the Institute of Medicine of the National Academies' Committee on Sports-Related Concussions in Youth—Dr McCrea, Dr Apps and other clinical colleagues have made baseline concussion testing accessible for young athletes statewide. Recommended by the American Academy of Pediatrics, baseline testing allows clinicians to compare brain function before and after injury, resulting in better care, return-to-play decisions and outcomes.

Such efforts are part of MCW's integrated concussion program, which is built on partnerships connecting Froedtert, The Medical College of Wisconsin, Children's Hospital of Wisconsin and the Zablocki VA Medical Center. The program demonstrates our commitment to advancing the clinical care of concussion to benefit people throughout Wisconsin and beyond.

Awareness about concussions has probably never been higher. It is the responsibility of physicians and medical researchers to make sure momentum translates into progress on the diagnosis, treatment and outcomes of mild traumatic brain injuries.

The Paul Coverdell National Acute Stroke Registry Comes to Wisconsin

Dorothy Bluma, RN; Jay A. Gold, MD, JD, MPH

The adage "time is muscle" is a familiar one within the medical community and to many patients as it pertains to a sudden cardiac events. However, the phrase "time is brain" is less recognized among the public, and it ought to be. As the third-leading cause of death in the United States, stroke causes staggering morbidity. More than 700,000 Americans per year have a stroke, with 15%-30% of those affected becoming permanently disabled.

Background

In the year 2000 Senator Paul Coverdell of Georgia suffered a fatal stroke. The following year Congress assigned the Centers for Disease Control and Prevention (CDC) the task of creating statewide stroke registries named after Senator Coverdell. The Paul Coverdell National Acute Stroke Registry (PCNASR) was inaugurated. These registries were to focus on improving quality of care within the states that were allocated to the project.

Initially, the CDC worked with stroke specialists across the United States to ascertain where the gaps in stroke care existed. As in other clinical areas, there were many gaps between recommended best practices and actual care being delivered across the care continuum. To begin closing these quality gaps the CDC, in June 2004, awarded grants to 4 states: Georgia, Illinois, Massachusetts, and North Carolina. The state health departments in these states formed lasting partnerships with the CDC. Furthermore, collaboration with The Joint Commission and the American Heart Association/American Stroke Association (AHA/ASA) took place. These affiliations allowed for the following 10 consensus measures to be developed:

1. STK-1 Venous Thromboembolism (VTE) Prophylaxis—Patients with an ischemic stroke or a hemorrhagic stroke who received VTE prophylaxis or have documentation why no VTE prophylaxis was given the day of or the day after hospital admission.
2. STK-2 Discharged on Antithrombotic Therapy—Patients with an ischemic stroke prescribed antithrombotic therapy at discharge.
3. STK-3 Patients with Atrial Fibrillation/Flutter Receiving Anticoagulation Therapy—Patients with an ischemic stroke with atrial fibrillation or flutter discharged on anticoagulation therapy.
4. STK-4 Thrombolytic Therapy—Acute ischemic stroke patients who arrive at the hospital within 120 minutes (2 hours) of time last known well and for whom IV tPA was initiated at this hospital within 180 minutes (3 hours) of time last known well.
5. STK-5 Antithrombotic Therapy by End of Hospital Day 2—Patients with ischemic stroke who receive antithrombotic therapy by the end of hospital day 2.
6. STK-6 Discharged on Statin Medication—Ischemic stroke patients with LDL ≥100, or LDL not measured, or, who were on cholesterol-reducing therapy prior to hospitalization are discharged on statin medication.
7. STK-7 Dysphagia Screening—Patients with ischemic or hemorrhagic stroke who undergo screening for dysphagia with an evidence-based bedside testing protocol before being given any food, fluids, or medication by mouth.
8. STK-8 Stroke Education—Patients with ischemic or hemorrhagic stroke or their caregivers who were given education and/or educational materials during the hospital stay addressing all of the following: risk factors for stroke, warning signs for stroke, activation of emergency medical system, need for follow-up after discharge, and medications prescribed at discharge.
9. STK-9 Smoking Cessation Counseling—Patients with ischemic or hemorrhagic stroke with a history of smoking cigarettes, who are, or whose caregivers are, given smoking cessation advice or counseling during hospital stay. For the purposes of this measure, a smoker is defined as someone who has smoked cigarettes anytime during the year prior to hospital arrival.
10. STK-10 Assessed for Rehabilitation—Patients with an ischemic stroke or hemorrhagic stroke who were assessed for rehabilitation services.

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Ms. Bluma is a stroke specialist. Doctor Gold is senior vice president and chief medical officer for MetaStar, Inc. This material was prepared by MetaStar, the Medicare Quality Improvement Organization for Wisconsin, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the US Department of Health and Human Services. The contents presented do not necessarily reflect CMS policy.

Upon hospital-based implementation and evaluation of these guidelines, statewide improvements in care were noted. At the end of the initial 3-year period, 180 hospitals were registered in the program and over 45,000 inpatients benefited. In July 2007, the CDC awarded funds to additional states, and in September 2012, other states including Wisconsin were added. There currently are 11 states participating in PCNASR.

Mission, Goals, and Objectives

The mission of the PCNASR is to:

1. Measure, track, and improve the quality of care for acute stroke patients.
2. Increase public awareness of stroke treatment and prevention.
3. Through secondary prevention, decrease the rate of premature death and disability from acute stroke.
4. Reduce disparities in acute stroke care by providing underserved populations with better access to high-quality care.

Wisconsin has developed an integrated collaborative approach to meet this mission with resources and expertise from MetaStar along with the CDC, the Department of Health Services, AHA/ASA, the Wisconsin Stroke Committee (WSC), Primary Stroke Centers and Emergency Medical Services (EMS) in Wisconsin. Wisconsin's goals are to:

1. Reduce death and disability due to heart disease and stroke and eliminate disparities in care.
2. Increase the quality of EMS care for possible stroke patients.
3. Improve the transition of care from EMS to hospital emergency department staff.
4. Improve the quality of acute and sub-acute hospital stroke care through adherence to established guidelines and endorsed quality measures.

There are multiple plans to assist hospital teams in achieving these goals. First-year aims are to have 20 hospitals participating in the PCNASR; at this writing 15 have shown interest. The participating facilities will enter data into AHA/ASA's "Get with the Guidelines" secure data network. These data then can be analyzed for quality improvement initiatives. The WSC, which encompasses caregivers from the stroke continuum of care, will develop the Wisconsin Stroke Plan to further statewide stroke initiatives. Partnerships with EMS will be established: the Wisconsin Ambulance Run Data System will be utilized to analyze data, which will be employed to enhance EMS systems. Participating hospitals will develop and implement quality improvement strategies. Statewide awareness initiatives of blood pressure control will occur in subsequent years.

Opportunity

Wisconsin has a remarkable opportunity to enhance the best practices related to stroke across the care-continuum for residents. The collaboration and efforts of experts in their fields from multiple organizations throughout the state will ensure the success of the Coverdell program.

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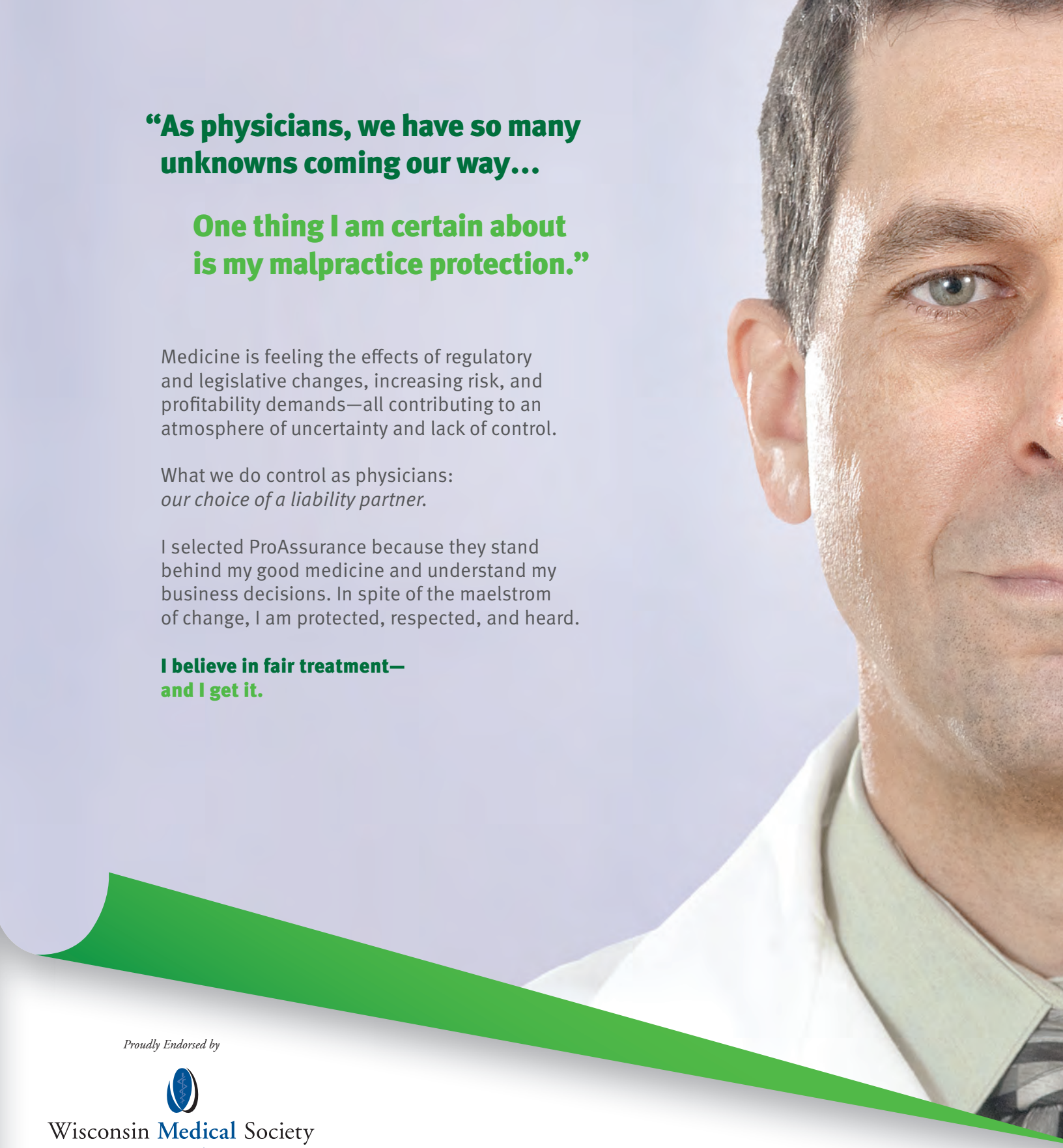

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