Should Language Matter Less to Journals?

Erik von Elm

PLoS Medicine now encourages translations in languages other than English; this decision can only be welcomed.

German-speaking readers are pleased by the novelty of a PLoS title written in their language. The Editorial starts with the first line of the well-known German poem “Lorelei” by Heinrich Heine (1797–1856) [1]. This year commemorates the 150th anniversary of his death. Originating from Germany, Heine was an early European citizen and a mediator between cultures. After traveling through Europe for years, he settled down in Paris. There he wrote the “Lorelei” and other poems in German while his essays in French made German literature known to the francophone public.

In Heine’s time, the question which language would prevail in science was yet undecided. In the 19th and the early 20th centuries pivotal works in different disciplines were published in languages other than English, as evidenced in the biographies of the Nobel Prize laureates (http://nobelprize.org). It seems that insufficient knowledge of the one foreign language did not impede an academic career at that time.

Today, proficiency in English is a luxury for many users of scientific information, as pointed out in the Editorial. The same is true for the non-anglophone researchers, who invest time and money in English courses only to try to communicate with their anglophone peers on equal linguistic terms.

Can scientific journals do more to overcome the existing language barriers in the meantime? Sure, they can allow the translation of their papers in other languages. But would they also trouble to employ smart machines or humans in order to translate a manuscript written in one of Heine’s languages into English before sending it out for peer review?

By the way, an English translation of the “Lorelei” is available at http://www.usd.edu/eric/deutsch/literatur/projekt/works/heine-lorelei.html.

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Fetal Alcohol Syndrome and Essential Fatty Acids

Undurit N. Das

Essential fatty acids (EFAs) are structural components of the brain and influence nerve conduction and transmitter release and action [1]. Prostaglandins (PGs) derived from EFAs and polyunsaturated fatty acids (PUFAs) modulate nerve conduction and transmitter function. Ethanol (1) reduces blood linoleic acid (LA) levels; (2) blocks conversion of LA and gammalinolenic acid (GLA) to arachidonic acid (AA), as well as alphalinolenic acid (ALA) to eicosapentaenoic and docosahexaenoic acids (EPA and DHA, respectively), by inhibiting delta-6 and delta-5 desaturases; and (3) enhances the conversion of dihomo-gamma-linolenic acid (DGLA) to PGE1 [1].

Ethanol-enhanced interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) production suggest that immunological mechanisms play a role in ethanol-induced diseases. Cerebral cortex from chronic ethanol-fed rats showed up-regulation of inducible nitric oxide (iNOS), cyclo-oxygenase-2 (COX-2), IL-1-beta, and activation of transcription factors nuclear factor-kappa B (NF-kappa B) and AP-1—effects that increased both caspase-3 and apoptosis [2].

Brains of ethanol-treated mice show raised phospholipase-A2 and phospholipase-C activity [3] that can cause the release of AA, EPA, and DHA from membrane phospholipids. AA, EPA, and DHA form precursors to eicosanoids—lipoxins (LXs), resolvins, and neuroprotectin D1 (NPD1) [4]. LXs, resolvins, and NPD1 suppress IL-6 and TNF-alpha production. PGs, LXs, resolvins, and NPD1 precursor supplies are limited; therefore, when ethanol consumption is substantial, tissue concentrations of PUFAs decline, leading to a fall in the synthesis of various PGs, LXs, resolvins, and NPD1.

DHA and other PUFAs released from the membrane in response to neurotransmitters [5] activate retinoid X receptor (RXR) as PUFAs form ligands for the RXR [6]. DHA deficiency results in impaired spatial learning and other abnormalities [7]. RXR heterodimerization partners peroxisome proliferator-activated receptors (PPARs), liver X receptors, and farnesoid X receptors that are essential for regulating energy and nutritional homeostasis. PUFAs, being ligands for RXR and PPARs, modulate these and other regulatory events by binding to these nuclear receptor heterodimers.

AA, DHA, EPA, LXs, resolvins, and NPD1 have neuroprotective actions [4]; inhibit IL-6 and TNF-alpha production that is neurotoxic; and increase synthesis of endothelial nitric oxide (eNO), a neurotransmitter. When neurons are depleted of their PUFA content, as happens after high alcohol intake, formation of LXs, resolvins, and NPD1 will be suboptimal and, hence, neuronal death induced by TNF-alpha cannot be antagonized. This results in fetal alcohol syndrome (FAS).

Nicotinamide is necessary for delta-6 desaturase and enhances the formation of various PUFAs and their products [8], suggesting that the neuroprotective action of nicotinamide against ethanol-induced FAS, as described by Alessandro Ieraci and Daniel Herrera [9], could be attributed to its action on these lipid pathways.

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that nicotinamide prevents the activation of JNK and the N-methyl-N-nitrosourea-induced apoptotic cell death in rat photoreceptor cells [7].

Inhibition of the phosphatidylinositol-3-kinase (PI3-K)/Akt pathway is another cell death mechanism associated with the translocation of Bax [8]. Administration of ethanol decreases the activation of Akt in the developing postnatal rat brain [6]. Nicotinamide is able to increase the activation of Akt in primary hippocampal neuronal cell cultures, and this is necessary to protect against oxygen-glucose-deprivation (OGD)-induced apoptosis [9].

Several studies have pointed out that ethanol exposure increases the generation of reactive oxygen species in the developing brain [10]. Nicotinamide has been shown to act directly at the mitochondrial level by preventing the enhancement in mitochondrial permeability transition (MPT) pore opening and the release of cytochrome-c following exposure to OGD [9].

Cellular energy metabolism is another significant factor that controls MPT pore formation, as the maintenance of mitochondrial membrane potential is an ATP-facilitated process. During oxidative stress, depletion of NAD, necessary for the production of ATP, is a critical step in precipitating cell death due to compromised energy supply. Nicotinamide administration increases the amount of NAD in the brain, and prevents its depletion and the consequent decrease of ATP [11].

We have demonstrated that nicotinamide prevents the ethanol-induced release of cytochrome-c and the following caspase-3 activation in brain development [2].

In conclusion, nicotinamide can prevent neuronal cell death by acting at different and probably complementary molecular levels.

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Unique Author Identification Number in Scientific Databases: A Suggestion

Matthew E. Falagas

There is an increasing trend toward the use of electronic databases of scientific information, such as the PubMed database of the National Library of Medicine and the various databases of the Institute for Scientific Information (ISI). These databases are frequently used nowadays for various purposes, including the peer-review process of papers submitted for publication in scientific journals. Most of the scientific journals now use a Web-based peer-review system that offers editors, peer reviewers, and publishers the capability to check the previous papers published by authors submitting a manuscript for consideration for publication [1]. In addition, these databases are frequently searched in an attempt to select potential speakers for scientific conferences and to obtain data for possible collaborators for a multicenter study, as well as in the process of evaluating the research productivity of scientists—which is being used for various purposes.

However, it is widely known that a considerable proportion of authors share the same last name and first initial. This seems to be the case for people of most ethnic heritages. In addition, authors of scientific publications do not frequently use their middle initial, which contributes to the confusion regarding the assignment of publications to the appropriate author. Frequently, it takes considerable effort and time to assign publications to the appropriate authors, particularly if there are authors that share the same last name and first initial (with or without the middle initial). This is usually based on the pattern of research interests, as well as the institutional affiliations of the various authors with the same name. In fact, this task is often impossible.

In order to decrease the problems arising from authors with identical names, I suggest the introduction of a unique author identification number (UAIN) in modern electronic databases of scientific information. I further suggest that such an identification number may be hidden in the electronic databases, i.e., it is not necessary for the UAIN to appear when reviewing the record of a publication. This function of the electronic databases could start operating after the providers of the databases are given a reasonable time to prepare. To avoid the resources needed to update the electronic databases with the appropriate assignment of publications to each author, I suggest that the UAIN not be used retrospectively. In this case, the record of publications for a specific author would be divided into two parts. The publications that are prospectively connected to a given author with a specific UAIN would have an indicator denoting this, while older publications (before the introduction of the UAIN) would not have such an indicator.

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Mistrust among Minorities and the Trustworthiness of Medicine

Matthew K. Wynia, Vanessa Northington Gamble

David Wendler and colleagues [1] have provided important data to help understand disparities in access to medical research among minorities. It is unfortunate, however, that they draw an unwarranted conclusion from a set of extremely heterogeneous studies. Worse still, by suggesting that the substantial body of research demonstrating how common it is for African Americans to mistrust the health-care system [2–4] is wrong, the authors imply that we do not need to come to terms with why this mistrust exists and how it should be addressed by the medical profession.

Wendler et al. note the extreme heterogeneity of the trials included in their study, but they ignore how much this affects the reliability of the metaanalytic techniques they employ. First, the vast majority of the “more than 70,000” patients studied was only involved in survey research—where large differences in response rates between races are not generally seen. Looking only at the clinical trials, the numbers are much smaller and the data become much more difficult to summarize. Among the seven surgical intervention trials studied, two have statistically significant differences between minority enrollment and white enrollment. In one, whites had about 2.7 times greater odds of enrollment than minorities, while in the other, minorities had about 1.6 times greater odds of enrollment than whites. In the ten clinical trials studied, three had statistically different enrollment rates; they, too, had greatly diverging results. For the most part, though, the clinical trials that Wendler et al. examined enrolled so few minority patients (in half of the studies, fewer than 50 minority patients were even asked to enroll), and they are so vastly different in design and objectives that very little information can be reliably gleaned from pooling their results. In fact, one of the largest trials included—the Minority-Based Community Clinical Oncology Program (MBCCOOP) cancer trial, which included
more than 400 African Americans—was specifically designed to appeal to minority patients, making any assumptions about its generalizability to all medical research extremely suspect. It is well known that meta-analysis is subject to this sort of problem; statistical tricks simply can’t account for fundamental differences in studies.

Despite these scientific weaknesses, Wendler et al. are right to conclude that it is inappropriate to focus on changing African Americans’ attitudes of mistrust, but not because those attitudes don’t exist. Many minorities don’t feel welcome and respected within the health-care system. Those who do come in have already crossed a threshold of trust, at least with their individual doctor. Those who don’t come in, of course, will never have the opportunity to be asked to enroll in a clinical trial. Instead, the reason it would be inappropriate to focus on changing patient attitudes is because these attitudes of mistrust are based on a history of untrustworthy behavior by the health professions, which must be acknowledged and rectified. In other words, the medical profession should not focus on making minorities be more trustworthy; we should focus on ensuring that we are becoming trustworthy.

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Authors’ Reply
The letter by Matthew Wynia and Vanessa Northington Gamble is based on an unfortunate conflation of behavior and attitudes [1]. Our paper evaluated the often repeated claim that individuals from minority groups are less willing to participate in health research compared with non-Hispanic whites [2]. That is, we evaluated what individuals do, whether they give consent, when invited to participate in health research. We did not and did not claim to evaluate individuals’ attitudes toward these requests or toward those who make them.

Our findings, based on the existing empirical data, suggest that individuals from minority groups who are eligible and who are invited to participate agree to enroll in health research at rates similar to those of non-Hispanic whites. Wynia and Northington Gamble read this conclusion as a claim about individuals’ attitudes, as a denial of the “substantial body of research that demonstrates how common mistrust of the health-care system is among African Americans.” This conflation of individuals’ behavior related to research enrollment with their levels of trust in the health-care system is surprising given that our focus on individuals’ willingness to participate in research is described in the title, and described throughout the text. Indeed, in an attempt to avoid just this conflation, we explicitly wrote in the text that “we did not assess minority groups’ attitudes toward health research.”

Wynia and Northington Gamble also accuse us of ignoring the heterogeneity in the empirical data we found, and claim that “very little information can be reliably gleaned from pooling” these data. With this latter statement, we agree. As explained in the manuscript, the heterogeneity of the data suggests there is no simple relationship between one’s race or ethnicity and one’s willingness to participate in health research. While little else can be gleaned from these data, their very heterogeneity undermines the claim that individuals from minority groups are consistently less willing than non-Hispanic whites to participate in health research.

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Increasing the Participation: Another Factor

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The Perspective by Aziz Sheikh [1] has vividly highlighted the lack of involvement of ethnic minorities in research studies, focusing on identifying the factors responsible for it. Apart from possible factors already discussed, another important factor that needs to be taken into consideration is the number of illegal immigrants in the United States and the United Kingdom. There are approximately 7 million illegal immigrants in the US (about 10% of 69.96 million ethnic minorities), and the number is growing by half a million each year [2,3]. The UK also shares the same trend, with 500,000
illegal immigrants (about 10.86% of 4.6 million ethnic minorities) [4,5].

In this regard, the apprehension of being traced as illegal immigrants poses a definite barrier to participating in any research activity. It is indeed a sensitive issue. Similar to the doctor–patient relationship, a confidential channel should be ensured between the researcher and the participant. It is the duty of the researcher to explain during the time of consent that this research has nothing to do with participants’ citizenship status, and no information will be used in any way against them. Legislation must be passed to provide legal immunity to all participants regardless of their legal status. I believe adopting such methodology will increase the number of participants belonging to ethnic minorities. Moreover, research would be carried out on a truly representative structure of the local population.

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