similar to that of your work. We think that most of the papers that studied the association HCV – DM suffer from selection bias. That is, in most of those papers, the subjects enrolled in the study have HCV diagnosed because they had elevated ALT and/or AST (quite common in HCV diagnostic pathway to evaluate HCV only if there are abnormal ALT and/or AST). High ALT/AST are often due to non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH), which are associated with DM (3). High ALT/AST more frequent in HCV and associated with DM are a confounder of the association HCV–DM. In our paper, we screened a random population sample for HCV, eliminating this type of selection bias *a priori*. Furthermore, we stratified and controlled for ALT in the statistical models in table 4, evidencing and eliminating the bias *a posteriori*. This type of selection bias can happen not only in case–control/cross-sectional studies, but also in cohort studies, and can be eliminated either by design, assembling carefully the cohort (screening for HCV, for example), or statistically, controlling for the selection variable stratifying or modeling. Thanks for giving us with your letter the opportunity to explain better our results.

In our paper, DM is associated inversely with female gender (table 3 and table 4—model B). However, we did not study the interaction of HCV with gender, therefore we do not know if female gender protects subjects with HCV from DM more than male gender.

Anti-HCV antibodies taken in 1985 were measured retrospectively (4). We thank the Authors of the letter for clarifying that point of our paper.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Manickam P, Muthusamy AK, Cappell MS *et al.* Association of chronic hepatitis C and diabetes: is there a gender difference?. Am J Gastroenterol 2013;108:1804-5 (this issue).
2. Montenegro L, De Michina A, Misciagna G *et al.* Virus C hepatitis and type 2 diabetes: a cohort study in Southern Italy. Am J Gastroenterol 2013;108:1108–11.
3. Masuoka HC, Chalasani N. Nonalcoholic fatty liver disease: an emerging threat to obese and diabetic individuals. Ann NY Acad Sci 2013;1281:106–22.
4. Osella AR, Misciagna G, Leone A *et al.* Epidemiology of hepatitis C virus infection in an area of Southern Italy. J Hepatol 1997;27:30–5.

[1]Laboratory of Epidemiology, Epidemiology Unit, National Institute for Digestive Diseases, IRCCS "Saverio de Bellis", Castellana, Bari, Italy; [2]Gastroenterology Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), University of Bari, Hospital Policlinico, Bari, Italy. Correspondence: G. Misciagna, MD, PhD, Epidemiology Unit, National Institute for Digestive Diseases, IRCCS "Saverio de Bellis", Castellana, Bari, Italy. E-mail: gmisciag@libero.it

Non-Celiac Wheat Sensitivity Is Not a New Entity

Eduardo Cueto Rúa, MD[1], Ricardo Drut, MD[2] and Amado Salvador Peña, MD, FRCP, AGAF[3]

doi:10.1038/ajg.2013.307

To the Editor: Carroccio *et al.* (1) have performed an excellent study and contributed to the differential diagnosis between celiac disease and gluten sensitivity. However, the title of their article is not entirely correct as they have claimed to have explored "a new clinical entity". In 1980, Trevor Cooke's group in Birmingham, UK, described very clearly patients with gluten-sensitive diarrhea without evidence of celiac disease (2). We have observed children and adult patients with chronic diarrhea, bloating, abdominal pain, nausea, headaches, with normal small intestinal biopsy specimens, and absence of celiac disease antibodies who responded dramatically to a gluten-free diet. At the present time, it seems that non-celiac wheat or gluten sensitivity may not be an entity but a syndrome as there is some evidence that the pathogenesis of this non-celiac gluten sensitivity is diverse in different patients. It is clear that few children and adults may suffer from gluten allergy where immunoglobulin-E is involved, but in the rest of the patients the intolerance may be manifested by abnormal permeability and abnormalities in the innate immunity (3,4) and yet another group by intolerance to other components of wheat and not related to the presence of celiac-toxic peptides (5).

One of us (ECR) has used to classify patients with non-celiac gluten sensitivity by the eponym of Cooper's disease in honor to the first author of the 1980 article. In retrospect, we believe that this entity or syndrome can be called Cooper and Cooke to pay credit to the long-life dedication of Trevor Cooke's to small intestinal disease and for having so clearly documented gluten-sensitive diarrhea without evidence of celiac disease or gluten allergy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Carroccio A, Mansueto P, Iacono G *et al.* Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Am J Gastroenterol 2012;107:1898–906.
2. Cooper BT, Holmes GK, Ferguson R *et al.* Gluten-sensitive diarrhea without evidence of celiac disease. Gastroenterology 1980;79:801–6.
3. Brottveit M, Beitnes AC, Tollefsen S *et al.* Mucosal cytokine response after short-term gluten challenge in celiac disease and non-celiac gluten sensitivity. Am J Gastroenterol 2013;108:842–50.
4. Sapone A, Lammers KM, Casolaro V *et al.* Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med 2011;9:23.
5. Biesiekierski JR, Newnham ED, Irving PM *et al.* Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am J Gastroenterol 2011;106:508–14.

[1]Department of Gastroenterology, Sor María Ludovica Hospital, Children Hospital, La Plata, Argentina; [2]Department of Pathology, Sor María Ludovica Hospital, Children Hospital, La Plata, Argentina; [3]Laboratory of Immunogenetics, Department of Medical Microbiology and Infection Control, "VU" University Medical Center, Amsterdam, The Netherlands. Correspondence: Amado Salvador Peña, MD, FRCP, AGAF, Laboratory of Immunogenetics, Department of Medical Microbiology and Infection Control, VU University medical Center, 1007 MB Amsterdam De Boelelaan 1117 Amsterdam, NH 1041 HV, The Netherlands. E-mail: pena.as@gmail.com

Response to Cueto Rúa *et al.*

Antonio Carroccio, MD[1], Alberto D'Alcamo, MD[2] and Pasquale Mansueto, MD[2]

doi:10.1038/ajg.2013.311

To the Editor: We thank Cueto Rúa *et al.* (1) for their interest in our work and for the comments about the paper of Cooper *et al.* (2) published in *Gastroenterology* more than 30 years ago. We fully agree with their opinion that the nine patients described in that paper could have suffered from non-celiac wheat sensitivity (NCWS). In fact, Cooper *et al.* (2) described patients with severe diarrhoea and abdominal pain, whose symptoms disappeared on gluten-free diet and reappeared on gluten challenge (both on open and double-blind challenge). The duodenal histology of these cases showed normal villi/crypts ratio, with an increase of the intra-epithelial lymphocytes. Although the Marsh (3) classification of the duodenal lesions in celiac disease (CD) came more that 10 years later, we can suppose that Cooper's patients had a Marsh 1 duodenal lesion. Thus, we agree that the above quoted are clinical and histological characteristics very similar to those we described in our patients (4). It is also intriguing that Cooper described a small group of patients who were all females. We also found that about 80% of the 276 patients we studied were females.

However, at the time of the Cooper study, the role of serology in CD diagnosis was minimal but nowadays we consider the presence of positive serum CD-specific antibodies as one of the criteria for a confident CD diagnosis. We recall the studies that demonstrated a clinical course in CD patients with Marsh 1 duodenal lesion and positive serum anti-transglutaminase antibodies identical to those with typical Marsh 3 lesions (5). This implies that the patients described by Cooper *et al.* (2) could have been suffering from what we now classify as potential CD (6).

Furthermore, it seems increasingly evident that the "world of NCWS patients" is composed of different kind of patients, with different pathogenic mechanisms of their disease. We described at least two subgroups, one showing clinical characteristics more similar to the CD patients and another more frequently having characteristics more similar to the allergic patients. Biesiekierski *et al.* (7) very recently published a paper that poses doubts about the real existence of NCWS and underlines a possible role of the fermentable, oligo-, di-, monosaccharides, and polyols (FODMAPs) as determining factors of the gastrointestinal symptoms in people self-reporting wheat-related problems. This latest study, however, excluded the patients with duodenal lymphocytosis who, on the contrary, were the focus of our and Cooper's studies (2,4). This could be another subgroup of NCWS patients. However, in our opinion, it is very unlikely that the "FODMAPs theory" can clear up the extra-intestinal manifestations related to wheat ingestion, which many patients report (8).

In conclusion, we think that we need to explore a new clinical entity in the coming years, that of wheat-related problems not linked to CD- or immunoglobulinE-mediated wheat allergy. Different subgroups of patients will probably be classified. The patients described in Cooper's excellent and pioneering study would probably be included in one of these NCWS "categories".

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Cueto Rúa E, Drut R, Salvador Peña A *et al.* Non-celiac wheat sensitivity is not a new entity. Am J Gastroenterol 2013;108:1805–6 (this issue).
2. Cooper BT, Holmes GK, Ferguson R *et al.* Gluten-sensitive diarrhoea without evidence of celiac disease. Gastroenterology 1980;79:801–6.
3. Marsh M. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330–54.
4. Carroccio A, Mansueto P, Iacono G *et al.* Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Am J Gastroenterol 2012;107:1898–906.
5. Kurppa K, Collin P, Viljamaa M *et al.* Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. Gastroenterology 2009;136:816–23.
6. Ludvigsson JF, Leffler DA, Bai JC *et al.* The Oslo definitions for coeliac disease and related terms. Gut 2013;62:43–52.
7. Biesiekierski JR, Peters SL, Newnham ED *et al.* No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology 2013;145:320–8.
8. Sapone A, Bai JC, Ciacci C *et al.* Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med 2012;10:13.

[1]Department of Internal Medicine, Hospital of Sciacca, ASP Agrigento, University of Palermo, Palermo, Italy; [2]Department of Internal Medicine, University of Palermo, Palermo, Italy. Correspondence: Pasquale Mansueto, MD, Department of Internal Medicine, University of Palermo, Via del Vespro, 141, Palermo 90127, Italy. E-mail: pasquale.mansueto@unipa.it

Estimated Short-Term Mortality Following TIPS Insertion for Patients With Hepatic Hydrothorax

R. Parker, MB[1,2], M.J. Armstrong, MB[1,2], I.A. Rowe, MB, PhD[1,2] and Diarmaid D. Houlihan, MB, PhD[1,2]

doi:10.1038/ajg.2013.290

To the Editor: We read with interest the study Dhanasekaran *et al.* (1). The authors document their experience of transjugular intrahepatic portosystemic shunt (TIPS) in 73 patients with hepatic hydrothorax. They identify pre-TIPS creatinine and MELD score as useful predictors of post-procedure survival. The 30-day mortality was 19%. Although AASLD guidelines suggest utility of TIPS in patients whose symptoms cannot be controlled by diuretics and sodium restriction, these data re-emphasize the potential for harm (2). Appropriate patient selection therefore remains critically important.

We have identified a significant error in this manuscript. Table 5 in the manuscript summarizes clinical data from retrospective studies examining the utility of TIPS in patients with hepatic hydrothorax. We note that the 30-day mortality is incorrectly reported for many of these studies. As early mortality following TIPS insertion most likely represents a direct complication of the procedure, the reported data may deter physicians from this therapeutic option. Using available retrospective studies we have summarized the short-term (45 days) mortality following TIPS for hepatic hydrothorax.

A literature search was undertaken using MeSH terms "transjugular intrahepatic portosystemic shunt" and "hepatic hydrothorax" using the set operator AND. We included all studies reporting the efficacy