and escalate the quality of service conventional colonoscopy provides. Over the last decade, colonoscopy has assumed the leading role as a colorectal cancer screening strategy in the United States, but we have also learned not all colonoscopies are equal and focusing on and documenting colonoscopy quality leads to improved patient outcomes.[12,13] We should welcome these new technologies as a driving force for improvements in patient care and outcomes owing both to the inherent features of the innovation and to the stimulus it provides for improving existing practice. Thanks in part to the study by Rex et al, capsule colonoscopy is a reality in the United States. The focus in the future will be further assessments of where it belongs in the menu of screening options and the spotlight it provides for improving the quality of the imperfect gold standard, colonoscopy.

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On Stress and the Liver: A Chicken and Egg Conundrum

See "Association between psychological distress and liver disease mortality: a meta-analysis of individual study participants," by Russ TC, Kivimäki M, Morling JR, et al, on page 958.

A theme common to contemporary pathophysiology is that we are constantly being bombarded by stressors that have deleterious effects on organ structure and function. Perhaps, the most frequently cited of these is 'oxidative stress,' for which a recent PubMed search revealed no fewer than 138,776 citations, with >64,000 published within the past 5 years.

Stress ascribed to reactive oxygen species (ROS) is well-known and has been much studied. It is a cost of our existing in an oxygen-rich environment and enjoying the benefits of oxidative phosphorylation by mitochondria for efficient synthesis of adenosine triphosphate.[1–4] Of course, antioxidant systems and principles have also evolved to protect us from the potential toxicities of superoxide and hydroxyl radicals, hydrogen peroxide, and other ROS. In addition to oxidative stress, other causes of metabolic stress and stress to the endoplasmic reticulum and other cellular organelles and components abound and, in recent years, have received increasing attention and study.[5,6]

Among the many factors that increase oxidative stress on hepatocytes and other types of liver cells are alcohol, especially by way of its induction of and metabolism by CYP

2E1, a rich source of ROS,[7,8] hepatitis C virus, iron,[9,10] and the injury caused by ischemia followed by reperfusion, as occurs with shock liver or liver transplantation. The metabolic syndrome also is involved in increasing oxidative and other stress to the liver. Indeed, this syndrome is now the most prevalent and frequent cause of liver injury in the United States and other affluent countries, and its prevalence is increasing rapidly in developing countries as well. Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome, which is characterized by obesity, glucose intolerance, insulin resistance, systemic arterial hypertension, increased risk of coronary artery, and other atherosclerotic cardiovascular disease. With the recent advent of highly effective direct-acting antiviral therapies for chronic hepatitis C, and with the continuing dearth of effective therapies for NAFLD and the metabolic syndrome, it seems inevitable that, within the next few years, NAFLD will eclipse chronic hepatitis C as the principal chronic liver disease causing excess and early morbidity, need for liver transplantation, and morbidity in the United States and elsewhere.

In this issue of *Gastroenterology*, Russ et al[11] from Great Britain and Australia provide evidence that psychological stress also is associated with and may somehow cause or contribute to progressive NAFLD and/or alcoholic liver disease (ALD).

Russ et al have recently published papers on adverse effects of psychological stress on overall mortality,[12] risk of dementia,[13] and arteriosclerotic cardiovascular disease.[14] Their methods have involved pooling data from as many as 16 cohort studies, carried out between the years 1994-2008 in England (13 annual surveys) and Scotland (3 surveys, carried out in 1995, 1998, and 2003). Russ et al now have turned their attention to associations between psychological stress and death ascribed to liver disease. They evaluated psychological stress with use of a 12-question instrument to assess general psychological health (GHQ-12). This instrument was devised in Great Britain by removal of items endorsed by physically ill respondents to a longer GHQ-60 instrument. The precise questions and scoring are available, but usually only for a fee [http://www.gl- assessment.co.uk/products/general-health-questionnaire/faqs?css=1]. Russ et al summarized information about psychological stress derived from responses to these 12 questions, graded according to a 4-point Likert scale (1–4, roughly corresponding with none, mild, moderate, or severe). Summary scores of $\geq$4 have been validated to indicate psychological stress, especially anxiety and depression, whereas scores of $<$4 have indicated little or no psychological distress.[15]

In their current work, they somewhat arbitrarily but reasonably divided respondents into 4 groups of increasing psychological stress, namely, those with scores of 0 (asymptomatic), 1–3 (subclinical stress), 4–6 (mildly symptomatic), and 7–12 (severely symptomatic). Russ et al also had information on their subjects' ages, genders, years after leaving full-time education (taken as a surrogate for level of formal education), occupational social class (taken as a surrogate for socioeconomic status), use of alcohol, tobacco, body mass index, and, in some, presence or absence of diabetes mellitus, weekly physical activity, and use of antihypertensive medications. Objective data recorded in all subjects included blood pressure, levels of gamma-glutamyl transpeptidase, total and high-density lipoprotein cholesterol, and C-reactive protein in the serum.

A strength of the study of Russ et al is that it includes data from 199,504 subjects, although 23,383 (12%) did not consent to linkage of their GHQ results to health outcomes, as provided by the British National Health Service database. Excluded from analyses were 3,201 subjects with missing consent forms or data about causes of death and 6,289 in whom results of GHQ-12 were missing. Still, their final cohort of 166,631 subjects was sizable and statistically powerful.

The primary outcome was all liver-related mortality, derived from the mortality data from the British National Health Service for ICD-9 or ICD-10 codes that include the great majority of liver diseases. In secondary analyses, they investigated separately the liver disease categories NAFLD, ALD, and 'all other'; persons who consumed no alcohol; and effects of covariates that had been measured only in some of the years (physical activity, systemic arterial hypertension, and serum analytes).

During a mean (SD) duration of follow-up of 9.5 (4.3) years, 17,368 subjects (10.4%) died, among whom 457 died of liver disease (2.6% of those who died or 0.27% of the total cohort analyzed). NAFLD accounted for 184 (40%) and ALD for 175 (38%) of liver-related deaths. The fully adjusted hazard ratio (HR) for death owing to liver disease in the group with the highest degree of psychological stress—GHQ scores of 7–12—was 2.59 (95% CI, 1.82-3.68). There was a monotonically increasing HR for death owing to liver disease as the level of stress increased from none to severe, although the CIs were large and overlapping one another, except for the lowest (GHQ scores 0-2) versus the highest (GHQ scores 10-12; see Figure 2 in Russ et al[11]). These correlations persisted after adjustment for degree of physical activity and/or smoking, and they were even stronger for the cohort with liver disease ascribed to NAFLD. In addition, the age-and sex-adjusted HRs were greater in the presence of obesity (HR, 1.28; 95 % CI 0.97-1.70), diabetes mellitus (HR, 2.83; 95 % CI, 1.83-4.41), and systemic arterial hypertension (HR, 1.94; 95 % CI, 1.45-2.59). The main conclusion of the work is that psychological stress, especially the presence of anxiety and depression, should be added to the stressors associated with increased risks of mortality owing to liver disease, especially NAFLD and/or ALD. (Other etiologies of liver disease were too uncommon to allow for statistically meaningful analyses.)

Strengths of the Russ et al study include the large number of subjects studied by an experienced group of investigators who used a previously validated instrument (GHQ-12) and methods. Unlike meta-analyses of diverse independent publications, the methods and analyses used were the same throughout and were performed by the same investigators, increasing confidence in the results. Limitations include the lack of assessment for liver disease at baseline and the few laboratory variables studied. In particular, it is unfortunate that there were no measures of