Dear friends of clinical journal club - load the file down at https://www.mdc-berlin.de/cjc:

The *N Engl J Med* image of the week concerns a 69-year-old woman who presented to the emergency room after experiencing 2 weeks of dizziness. On physical exam she appeared jaundiced, and had hepatomegaly and generalized abdominal tenderness. Rectal exam showed silver-colored stool. She had a hemoglobin level of 7.5 g per deciliter (reference range, 11.0 to 14.5), an elevated total bilirubin level, and an elevated alkaline phosphatase level. What is the diagnosis? You are offered upper gastrointestinal bleeding, metastatic colon cancer, heavy-metal toxicity, liver cirrhosis, and Dubin-Johnson syndrome. Hint: the color of the stool is also known as Thomas's sign. Up to 2% of all cases of amyotrophic lateral sclerosis (ALS) result from mutations in the gene encoding superoxide dismutase 1 (SOD1). More than 180 different SOD1 mutations have been identified in ALS. The mechanisms by which mutations in SOD1 cause degeneration of motor neurons in genetic ALS are not fully understood; a toxic gain of function has been considered to be the most likely mechanism in ALS caused by SOD1 mutations. Lowering the concentration of mutant SOD1 protein may be a potential target for therapeutic intervention. Antisense oligonucleotides (ASOs) have been generally safe for the treatment of other diseases, including spinal muscular atrophy. Tofersen is an antisense oligonucleotide that mediates the degradation of superoxide dismutase 1 (SOD1) messenger RNA to reduce SOD1 protein synthesis. Intrathecal administration of tofersen is being studied for the treatment of amyotrophic lateral sclerosis (ALS) due to SOD1 mutations. Investigators conducted a phase 1–2 ascending-dose trial evaluating tofersen in adults with ALS due to SOD1 mutations. In each dose cohort (20, 40, 60, or 100 mg), participants were randomly assigned in a 3:1 ratio to receive five doses of tofersen or placebo, administered intrathecally for 12 weeks. The primary outcomes were safety and pharmacokinetics. The secondary outcome was the change from baseline in the cerebrospinal fluid (CSF) SOD1 concentration at day 85. Clinical function and vital capacity were measured. Tofersen was tolerated, intrathecal treatment causes discomfort, SOD1 activity decreased. In a second study, 2 ALS patients were given an adeno-associated virus intrathecally harboring a microRNA to suppress SOD1. One patient may have developed an immunological reaction to the treatment. He may have improved his leg strength

slightly but then died of ALS. Post-mortem, his SOD1 protein expression in the spinal cord appeared decreased. The second patient seemed to stabilize his course. He received immunosuppression and tolerated the adenoviral-mediated microRNA. Injuries from falls are major contributors to complications and death in older adults. Despite evidence from efficacy trials that many falls can be prevented, rates of falls resulting in injury have not declined. Investigators conducted a pragmatic, cluster-randomized trial to evaluate the effectiveness of a multifactorial intervention that included risk assessment and individualized plans, administered by specially trained nurses, to prevent fall injuries. A total of 86 primary care practices across 10 health care systems were randomly assigned to the intervention or to enhanced usual care (the control) (43 practices each). The participants were community-dwelling (at home) adults, 70 years of age or older, who were at increased risk for fall injuries. The primary outcome, assessed in a time-to-event analysis, was the first serious fall injury. The intervention, although well meaning, was of no value; intervention and control group fell at the same rate. Nemolizumab is a subcutaneously administered humanized monoclonal antibody against interleukin-31 receptor A, which is involved in pruritus and inflammation in atopic dermatitis. In phase 2 studies, nemolizumab lessened the severity of atopic dermatitis. In a 16-week, double-blind, phase 3 trial, investigators randomly assigned Japanese patients with atopic dermatitis and moderate-to-severe pruritus and an inadequate response to topical agents in a 2:1 ratio to receive subcutaneous nemolizumab (60 mg) or placebo every 4 weeks until week 16, with concomitant topical agents. The primary end point was the mean percent change in the visual-analogue scale (VAS) score for pruritus (range, 0 to 100, with higher scores indicating worse pruritus) from baseline to week 16. Blocking IL31A receptor signaling resulted in a greater reduction in pruritus than placebo over a period of 16 weeks in patients with atopic dermatitis who had not had an adequate response to topical agents and antihistamines. The *N Engl J Med* review is on degenerative cervical spondylosis and neurosurgical treatment options. In *Nature*, we inspect a review of >20 million Covid-19 patients and discover risk factors for survival. Age, male sex, obesity, deprivation (being poor), being “nonwhite”, diabetes, recent cancer, and decreased renal function indicated poorer outcomes. Of >17 million patients, >10,000 died (Mortality 0.6%; the rate is about 5 times higher than today’s influenza). The N Engl J

Med case of the week is a 76 year-old woman who dies of Covid-19. An autopsy is performed. The USA autopsy rate is <10%. I believe that at my institution it is <3%. We learn that even in an era with routine use of high-resolution imaging, published studies have shown that approximately 50% of autopsies reveal findings that were not suspected before death and 20% of autopsies lead to the diagnosis of a primary cause of death that was not established clinically. In the absence of an autopsy, the likelihood that a death certificate will be inaccurate is at least one in three. In the Lancet, we inspect variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 countries. Despite receiving less secondary prevention, women do not have worse cardiovascular disease outcomes. Vitiligo is a circumscribed loss of skin pigmentation, probably of autoimmune etiology. The condition is associated with autoimmune thyroid disease, diabetes mellitus, and pernicious anemia. Ruxolitinib (JAK-STAT pathway inhibitor) beat placebo in a randomized controlled trial. A comparative analysis of lifetime benefits from randomized trials for heart failure with reduced ejection fraction (HFrEF) indicates that Ang II-Neprilysin (ARNI), beta-blocker, MRA, and SGLT2 inhibitors in combination represent a new therapeutic standard for HFrEF. The Lancet review is on stroke. Much progress reported here! We close with a Gujarati woman who develops a very odd cause of encephalitis. She is apparently not a swimmer. The oral presentations will be in Wednesday at 16.00 English and 17.00 German.

Yours,

Fred Luft (Check out the file pdf at https://www.mdc-berlin.de/cjc)