Dear friends of clinical journal club - load the file down at https://www.mdc-berlin.de/cjc. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A 47-year-old man with type 2 diabetes presented to the endocrinology clinic owing to several years of progressive growth of skin lesions on his lower abdominal wall where he had repeatedly injected insulin. He also reported unpredictable episodes of hypoglycemia. A physical examination was notable for two pendulous skin masses on the lower abdominal wall. The glycated hemoglobin level was 9.2% (reference value, <7.1). What is the most likely diagnosis? You are offered: Inguinal hernias, Injection site granulomas, Insulin-derived amyloidosis, Lipoatrophy, and Lipomas. It's a dystrophy, not an atrophy. Daratumumab, an anti-CD38 monoclonal antibody, has been approved for the treatment of multiple myeloma. Data are needed regarding the use of daratumumab for high-risk "smoldering" multiple myeloma, a precursor disease of active multiple myeloma for which no treatments have been approved. In a phase 3 trial, investigators randomly assigned patients with high-risk smoldering multiple myeloma to receive either subcutaneous daratumumab monotherapy or active monitoring. Treatment was continued for 39 cycles, for 36 months, or until confirmation of disease progression, whichever occurred first. The primary end point was progression-free survival. The primary endpoint was met, even when smoldering. In a previous phase 2 trial, bacille Calmette–Guérin (BCG) revaccination was not shown to provide protection from primary Mycobacterium tuberculosis infection but prevented sustained M. tuberculosis infection, defined by an initial conversion on a QuantiFERON-TB (QFT) test (an interferon-γ release assay) from negative to positive, followed by two additional positive QFT tests at 3 and 6 months after the initial conversion (a secondary end point). A vaccine efficacy of 45% (95% confidence interval [CI], 6 to 68) was observed. Now, investigators performed a phase 2b, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of BCG revaccination, as compared with placebo, for the prevention of sustained QFT test conversion (primary end point) in QFT test–negative, human immunodeficiency virus (HIV)–negative adolescents. In essence, the investigators provided a "booster" in young people who had already been vaccinated with BCG. Unfortunately, the second

dose of BCG did not provide protection from QFT conversion. Children living with human immunodeficiency virus (HIV) have limited options for second-line antiretroviral therapy (ART). In an open-label trial with a 2-by-4 factorial design, investigators randomly assigned children with HIV who had first-line treatment failure to receive second-line therapy with tenofovir alafenamide fumarate (TAF)–emtricitabine or standard care (abacavir or zidovudine, plus lamivudine) as the backbone and dolutegravir or ritonavir-boosted darunavir, atazanavir, or lopinavir as the anchor drug. The study provides us with an acceptable second-line treatment option for HIV-infected children. What to do when your lymphoma patients no longer respond to your CAR-T cell therapy? The answer could consist of providing them with a second "armored" CAR. A promising strategy to improve CAR T-cell efficacy involves developing fourth-generation armored CAR T cells that secrete proinflammatory cytokines to bolster antitumor activity. This approach is currently being explored in solid tumors accordingly, to the hypothesis that cytokine secretion enhances the cytotoxicity of CAR and tumor-infiltrating T cells while modifying the immunosuppressive tumor microenvironment. One such cytokine, interleukin-18, is a proinflammatory molecule that is primarily produced by macrophages and dendritic cells. The "second-generation" armored CAR addressing CD-19 and providing IL-18 looks promising. The Philadelphia (Ph) chromosome is a balanced translocation of chromosomes 9 and 22 placing the Abelson tyrosine kinase adjacent to the breakpoint cluster region. Ph was first described in chronic myelocytic leukemia. However, Ph is also common in acute lymphoblastic leukemia (ALL). In the year 2000, a tyrosine-kinase inhibitor without chemotherapy was introduced for the frontline treatment of older adults with Ph-positive ALL, which gave rise to a new era in the management of this disease. N Engl J Med reviews this issue. The patient of the week has a sore throat and a retropharyngeal mass. In the Lancet the first issue is a worldwide study of sexual violence against children. We learn that the prevalence of this depressing condition is very high, worldwide. To my knowledge the sole drug approved to treat amyotrophic lateral sclerosis (ALS) is the glutamate antagonist, riluzole. Adding low doses of interleukin-2 (IL-2) could help. In a large, randomized trial, low-dose IL-2 had no statistically significant effect. Hepatocellular cancer is difficult to treat when nonresectable. Could checkpoint inhibition help? We learn that it could. The Lancet

review is on trachoma, a readily treatable disease that still causes blindness in some countries. The World Hypertension League suggest that hypertension should be diagnosed and treated in all health facilities. Science Magazine and Nature both draw attention to a Cell paper describing the structure of the glucose receptor on the tongue. Thus, human sweetness is revealed. We then visit the diving Korean women that make it down to 20 meters at 3 atmospheres of pressure without any outside assistance. They have a super genetically determined “diving” reflex. Join me on Wednesday, May 28 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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