Dear friends of clinical journal club - load the latest 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 6-month-old baby boy was transferred to a quaternary children's hospital for evaluation and management of seizures. One week earlier, he had had decreased oral intake, vomiting, and irritability. Laboratory testing showed hypocalcemia, hypophosphatemia, and microcytic anemia. Radiography of the left hand and wrist to evaluate hypocalcemia is shown. What is the most likely diagnosis? You are offered: Congenital syphilis, Hypoparathyroidism, Lead poisoning, Osteopetrosis, or Rickets. The bone films provide the answer. Pulmonary fibrosis causes pulmonary hypertension. Prostacyclines are approved for this condition. Two phase 3, randomized trials of inhaled treprostinil for idiopathic pulmonary fibrosis (IPF) were conducted based on preclinical and clinical evidence of an antifibrotic mechanism. TETON-2 was completed first, and results were published; the results of TETON-1 and of both trials combined are reported. In the double-blind TETON-1 trial, investigators randomly assigned patients with IPF to receive inhaled treprostinil or placebo (12 breaths four times daily). The primary end point was the change in forced vital capacity (FVC) at week 52. Secondary end points, which were analyzed in a prespecified order to control for multiplicity, were clinical worsening (the first occurrence of death from any cause, hospitalization for a respiratory cause, or a relative decline of ≥10% in the percentage of predicted FVC) and acute exacerbation of IPF (each assessed in a time-to-event analysis), survival, change in percentage of predicted FVC, quality of life, and change in diffusion capacity of the lungs for carbon monoxide at week 52. Treprostinil preserved FVC, compared to placebo. Next, N Engl J Med reports the next treprostinil trial, namely TETON-2. This study provided the same results as the TETON-1. Melanocortin 4 receptor (MC4R) is a G protein–coupled receptor expressed predominantly in the hypothalamus. MC4R is a key regulator of energy balance. Its ligands include peptide hormones derived from pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP). These peptides are secreted by neurons that respond to leptin and other hormonal signals reflecting nutritional status. In the fed state, activation of MC4R by α-melanocyte–stimulating hormone, which is derived from

POMC, reduces food intake, whereas in the fasted state, AgRP inhibits MC4R signaling to increase food intake. Genetic variants that impair MC4R signaling cause obesity, whereas variants that enhance MC4R signaling confer protection against obesity. MC4R agonists are approved for genetic causes of hypothalamic obesity. A phase 2 trial of the melanocortin-4 receptor agonist, setmelanotide, showed substantial weight loss in patients with acquired hypothalamic obesity, but additional data are needed. Investigators conducted a phase 3 trial in which participants were randomly assigned in a 2:1 ratio to receive setmelanotide (at a dose of 1.5 to 3.0 mg) or placebo administered subcutaneously once daily for 52 weeks after a dose-escalation period. Persons at least 4 years of age were potentially eligible for the trial if they had acquired hypothalamic obesity, which was defined by a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) that was at or above the 95th percentile for age and sex (for participants <18 years of age) or at least 30 (for participants ≥18 years of age) and a history of a hypothalamic tumor, lesion, or injury. The primary end point was the mean percent change in BMI from baseline to 52 weeks after the end of the dose-escalation period. Secondary end points included the mean change in the weekly average of the maximal daily hunger score, assessed in participants at least 12 years of age. Setmelanotide caused substantial weight loss in these patients with secondary (acquired) hypothalamic obesity. Anaplastic lymphoma kinase (ALK) inhibitors have emerged as promising agents for patients with resectable ALK-positive non–small-cell lung cancer (NSCLC). Whether ensartinib, a second-generation ALK inhibitor, is safe and effective in such patients is unknown. In a phase 3, double-blind, randomized trial involving patients with completely resected, ALK-positive stage IB to IIIB NSCLC after adjuvant chemotherapy, investigators randomly assigned patients to receive ensartinib at a dose of 225 mg once daily or placebo for 24 months. The primary end point was disease-free survival in patients with stage II to IIIB NSCLC. The key secondary end point was disease-free survival in the overall patient population. Disease-free survival was increased with ensartinib, compared to placebo. The N Engl J Med review is about nutrition in critically ill adults. The mystery patient of the week is a lung-transplant patient who develops fatigue, fever, and hypoxemia. At the time of lung procurement, a single granuloma in the left lower lobe was noted incidentally on chest imaging in the

donor. In the Lancet, we confront a randomized trial comparing orforglipron to dapagliflozin in obese patients with type-2 diabetes. Orforglipron won the contest, indicating that obesity drives type-2 diabetes. Next, Lancet investigators compared benzylpenicillin to flucloxacillin (or cloxacillin) in patients with penicillin-sensitive staphylococcal bacteremia (PSSA). Benzylpenicillin was probably “not worse” in patients with PSSA bacteremia. Earlier we learned that cefazolin is a better drug (MSSA) anyway. One of the drawbacks of fetal endoscopic tracheal occlusion (FETO) for congenital diaphragmatic hernia is the need for a second invasive intervention to re-establish airway patency. The ‘Smart-TO’ device is a new balloon for FETO that deflates spontaneously when placed in a strong magnetic field, therefore overcoming the need for a second procedure. The safety and efficacy of this device have not yet been demonstrated. A Lancet study establishes the safety and efficacy of the Smart-TO device. Next, Lancet provides an estimate how vaccination against papilloma virus has protected persons from cervical cancer. Lancet next presents a global collaboration to promote the health and wellbeing of children and future generations. Then, Lancet discusses a case of necrotizing encephalitis. In 2024, malaria resulted in more than 250 million cases and 550,000 deaths in Africa. Rural areas are typically most affected, especially during rainy seasons that provide abundant breeding sites for Anopheles mosquito vectors. First detected in Djibouti City in 2012, the invasion of Africa by the Asian malaria mosquito *Anopheles stephensi* has the potential to change the spatial and temporal distribution of malaria in Africa, undermining decades of malaria control progress. Science Magazine reports a genomic study on the spread of this mosquito. The Washington Post reports on the deep-fried contradiction of MAHA (make America healthy again) at the Great American State Fair. Not much promise here. No oral presentation on July 15. Load down the file and join me again on July 22.

Sincerely, Fred Luft

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