factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;310:2050–2060.

9. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, *et al.* Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373:1095–1105.

10. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, *et al.*; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375:919–931.

11. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, *et al.*; Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020;8:359–367.

12. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.

13. Pack AI, Magalang UJ, Singh B, Kuna ST, Keenan BT, Maislin G. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep (Basel)* 2021;44:zsaa229.

14. McEvoy RD, Sánchez-de-la-Torre M, Peker Y, Anderson CS, Redline S, Barbe F. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep (Basel)* 2021;44:zsab019.

15. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, *et al.*; Document Reviewers. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:e1–e160.

16. Haldar S, Khan HR, Boyalla V, Kralj-Hans I, Jones S, Lord J, *et al.* Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. *Eur Heart J* 2020;41:4471–4480.

⌀ A Ginger Root or Plum Model for the Tuberculosis "Granuloma"?

Many tuberculosis (TB) researchers tend to view lung lesions as largely spherical "granulomas" and cavities as granulomas that have become necrotic, expand, and erode into bronchi. Clinical TB pathologists and radiologists, on the other hand, are aware that this image is an oversimplification, partially induced by the shift from human autopsies to animal models for immunopathology studies. Pioneering clinical histopathology studies from the preantibiotic era showed that postprimary disease begins as infection of lipid-laden foamy alveolar macrophages and bronchiolar obstruction progressing to caseating cavitary disease. Dissemination primarily happens via bronchogenic rather than lymphatic and hematogenous spread (1–6). Radiologically, bronchiole and alveolus obstruction correspond to the tree-in-bud patterns commonly seen in computed tomography (CT) scans of adult TB, as shown in postmortem thin section CT (7). Over the past decade, the CT component of positron emission tomography (PET)-CT has revealed wide networks of connected lesions with complex morphology and bronchial thickening (8, 9), consistent with early studies.

In this issue of the *Journal*, Wells and colleagues (pp. 583–595) combine micro-CT (μCT) imaging, histology, and immunohistochemistry to confirm, refine, and extend these underappreciated immunopathology concepts (10). μCT merges high resolution in the single digit micron scale with the power of three-dimensional (3D) imaging to overcome the caveat of two-dimensional (2D) histology staining, which both underestimates the connection between lesions and overestimates the distance between key pulmonary structures such as blood vessels, airways, and diseased tissue. The authors first establish a correspondence between the cellular structures seen in 2D histology images and the appearance of lesion areas in μCT 3D reconstructions. Coregistering these two imaging modalities reveals complex ginger root–shaped lesion networks, oriented along airways and the vasculature, nicely illustrated in multiple supplemental videos. The 3D rendering of lesions connected and shaped by the bronchial tree suggests that airways are progressively replaced by lesions. To support this theory, the authors resort to immunohistochemistry and histology staining, showing obstructed bronchi with necrotic material, infected neutrophils and macrophages, and extracellular bacteria, spilling from granulomas into airways, indicating bronchogenic spread of both *Mycobacterium tuberculosis* bacilli and TB disease. Small nodules are mostly spherical, wheras larger ones adopt ginger root–like shapes, and epithelial cell remnants line the outside of granulomas, consistent with nodules expanding along and destroying the bronchial architecture (Figure 1). This expansion cooccurs with vascular pruning and hemorrhage in the close vicinity of lesions, compromising access to nutrients, anti-TB drugs, and oxygen.

A limitation of the study is the reliance on resected lungs from patients with TB who had long-term and severe drug-refractory disease. However, bronchial wall necrosis has also been observed in old and more recent postmortem studies (11). Complementing μCT with lower-resolution PET-CT (6) could overcome this potential limitation because PET-CT is noninvasive, can be pursued longitudinally starting before therapy initiation, and is not limited to individuals undergoing lung resection. Through systematic observational studies, the two methodologies could inform each other to determine how much the present findings can be generalized to less severe TB disease.

The prevailing viewpoint that plum-shaped granulomas are the key lesions of both primary and post-primary TB is an oversimplification. In animal models, TB granulomas often present as spherical or ovoid structures within the parenchyma, whereas caseous pneumonia is seldom observed, although this view could partially result from biases introduced by 2D histopathology studies and the short-term nature of most models. Bronchogenic spread is not rare in rabbits and nonhuman primates (12, 13), suggesting that mammalian models present characteristics of both primary and post-primary TB but may fail to
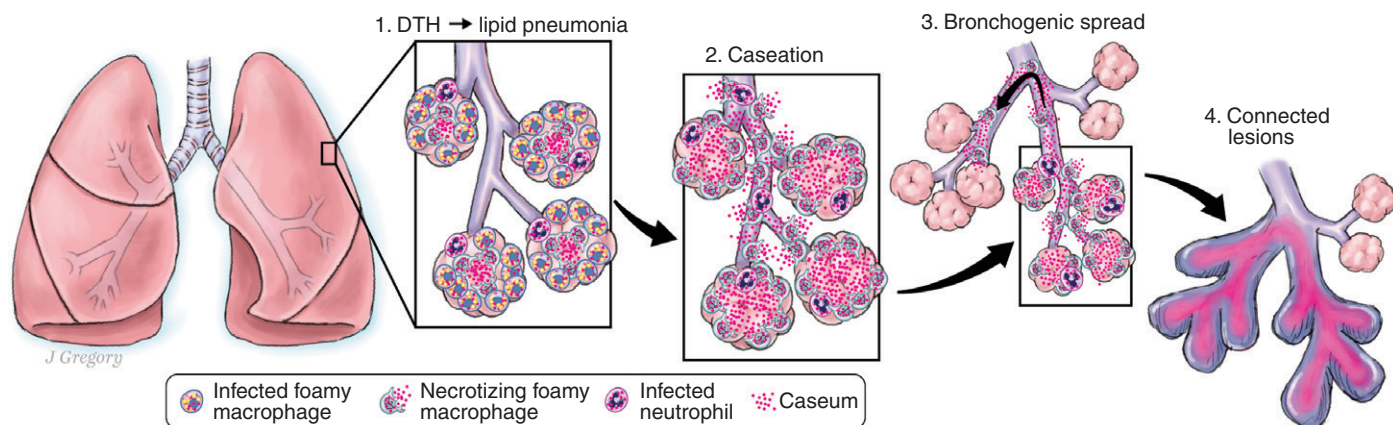
Figure 1. Tuberculosis lesions are connected. (*1*) One form of postprimary tuberculosis disease begins as lipid or lipoid pneumonia, with bacilli-laden foamy alveolar macrophages and neutrophils. (*2*) Bronchiolar obstruction and microvascular occlusion associated with delayed-type hypersensitivity leads to the formation of small caseating cavitary foci. (*3*) Dissemination primarily happens via bronchogenic spread. (*4*) Nodules grow along the bronchial tree and airways get progressively replaced by connected lesions oriented along the bronchial and vascular network, as visualized by the study of Wells and colleagues. DTH = delayed-type hypersensitivity. Illustration by Jill Gregory.

coordinate and align them as humans do (14). Other animal model features are reminiscent of the human findings described here but may not have been correctly interpreted in the absence of high-resolution 3D imaging methods. The study by Wells and colleagues (10) constitutes an opportunity to pursue formal μCT studies in animal models, to determine the extent of bronchogenic spread and bronchial wall necrosis, to establish their contribution to disease dissemination in each model, and to discover how models can be manipulated to better recapitulate selected aspects of human TB. For example, rapid-onset exudative lesions leading to cavities from dissolution of caseous pneumonia can be reproduced in rabbits by prior sensitization or immunization (15).

How do those findings impact the pharmacology of TB drugs? Despite our oversimplified view of granuloma progression (16), drug partitioning at the caseum–cellular interface remains a sound concept, but a purely lesion-centric model omits one important compartment: the lumen of airways where a mix of intracellular and extracellular bacilli is found in mobile necrotic material during bronchogenic spread. Importantly, these bacterial populations likely transit in and out of microenvironments that are nonpermissive to replication along the bronchial tree. This suggests that temporal and spatial microenvironment dynamics contribute to differential drug susceptibility, which should be taken into consideration when designing drug regimens. In addition, genetically resistant bacteria may not be as contained within individual cavities as previously thought.

Complex networks of connected lesions also make the case for inhalation drug delivery, at least in patients with extensive cavitary disease who require longer treatment duration to achieve cure (17). Given the radiological and pathological similarities between TB and nontuberculous mycobacterial (NTM) lung disease, this work provides an incentive to consider μCT studies in patients with NTM, as lung resection surgery is a therapeutic option for drug refractory cases. Administration of amikacin—a pillar of NTM disease therapy—by inhalation has become more widespread in clinical practice. Whether this comes with a therapeutic benefit and what the underlying mechanisms are remain to be formally established.

Concepts are the drivers of research. Using an elegant suite of multimodal imaging, Wells and colleagues (10) leverage the power of 3D μCT to reveal unprecedented high-resolution structures of human TB lesions and generate awareness that TB "granulomas" are more connected and complex than generally appreciated. The coordinated study of human TB pathology and disease progression in animal models, using a panel of CT-derived modern technologies, could help manipulate these models to address long-standing questions more adequately about host–pathogen relationships and the development of targeted therapeutics and vaccines. ∎

Véronique Dartois, Ph.D.
Center for Discovery and Innovation
Hackensack Meridian Health
Nutley, New Jersey
and

Department of Medical Sciences
Hackensack Meridian School of Medicine
Nutley, New Jersey

Thomas Dick, Ph.D.
Center for Discovery and Innovation
Hackensack Meridian Health
Nutley, New Jersey

Department of Medical Sciences
Hackensack Meridian School of Medicine
Nutley, New Jersey
and

Department of Microbiology and Immunology
Georgetown University
Washington, DC

ORCID IDs: 0000-0001-9470-5009 (V.D.); 0000-0002-9604-9452 (T.D.).

References

1. Hunter RL. Tuberculosis as a three-act play: a new paradigm for the pathogenesis of pulmonary tuberculosis. *Tuberculosis (Edinb)* 2016;97:8–17.
2. Dannenberg AM Jr. Pathogenesis of human pulmonary tuberculosis. Washington, DC: ASM Press; 2006.
3. Ulrichs T, Kaufmann SH. New insights into the function of granulomas in human tuberculosis. *J Pathol* 2006;208:261–269.
4. Canetti, G. The tubercle bacillus. New York: Springer Publishing Company; 1955.
5. Im JG, Itoh H, Lee KS, Han MC. CT-pathology correlation of pulmonary tuberculosis. *Crit Rev Diagn Imaging* 1995;36:227–285.
6. Chen RY, Yu X, Smith B, Liu X, Gao J, Diacon AH, *et al.* Radiological and functional evidence of the bronchial spread of tuberculosis: an observational analysis [published 2021 Jul 6; accessed 2021 Aug 17]. Available from: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00058-6/fulltext.
7. Im JG, Itoh H. Tree-in-bud pattern of pulmonary tuberculosis on thin-section CT: pathological implications. *Korean J Radiol* 2018;19:859–865.
8. Malherbe ST, Dupont P, Kant I, Ahlers P, Kriel M, Loxton AG, *et al.*; Catalysis Biomarker Consortium. A semi-automatic technique to quantify complex tuberculous lung lesions on ^{18}F-fluorodeoxyglucose positron emission tomography/computerised tomography images. *EJNMMI Res* 2018;8:55.
9. Chen RY, Dodd LE, Lee M, Paripati P, Hammoud DA, Mountz JM, *et al.* PET/CT imaging correlates with treatment outcome in patients with multidrug-resistant tuberculosis. *Sci Transl Med* 2014;6:265ra166.
10. Wells G, Glasgow JN, Nargan K, Lumamba K, Madansein R, Maharaj K, *et al.* Micro–computed tomography analysis of the human tuberculous lung reveals remarkable heterogeneity in three-dimensional granuloma morphology. *Am J Respir Crit Care Med* 2021;204:583–595.
11. Im JG, Itoh H, Shim YS, Lee JH, Ahn J, Han MC, *et al.* Pulmonary tuberculosis: CT findings—early active disease and sequential change with antituberculous therapy. *Radiology* 1993;186:653–660.
12. Blanc L, Sarathy JP, Alvarez Cabrera N, O'Brien P, Dias-Freedman I, Mina M, *et al.* Impact of immunopathology on the antituberculous activity of pyrazinamide. *J Exp Med* 2018;215:1975–1986.
13. Capuano SV III, Croix DA, Pawar S, Zinovik A, Myers A, Lin PL, *et al.* Experimental *Mycobacterium tuberculosis* infection of cynomolgus macaques closely resembles the various manifestations of human *M. tuberculosis* infection. *Infect Immun* 2003;71:5831–5844.
14. Hunter RL, Actor JK, Hwang SA, Khan A, Urbanowski ME, Kaushal D, *et al.* Pathogenesis and animal models of post-primary (bronchogenic) tuberculosis, a review. *Pathogens* 2018;7:E19.
15. Urbanowski ME, Ihms EA, Bigelow K, Kübler A, Elkington PT, Bishai WR. Repetitive aerosol exposure promotes cavitary tuberculosis and enables screening for targeted inhibitors of extensive lung destruction. *J Infect Dis* 2018;218:53–63.
16. Dartois V. The path of anti-tuberculosis drugs: from blood to lesions to mycobacterial cells. *Nat Rev Microbiol* 2014;12:159–167.
17. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, *et al.* A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018;24:1708–1715.