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Orson Welles as Harry Lime in *The Third Man*, produced and directed by Carol Reed, after a screenplay by Graham Greene.
Still courtesy of the British Film Institute

ROALD HOFFMANN
SHIRA LEIBOWITZ

MOLECULAR MIMICRY, RACHEL AND LEAH, THE ISRAELI MALE, AND THE INESCAPABLE METAPHOR IN SCIENCE

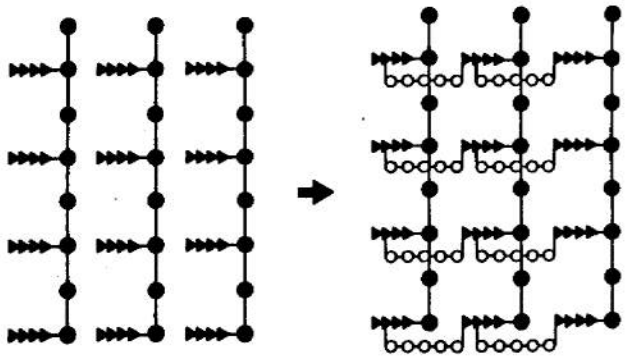
Roald Hoffmann begins: Isaac grew old and dim of sight. He wanted to impart the paternal blessing to the first-born of his twin sons, Esau. Jacob and his mother Rebecca connived to fool Isaac and cheat Esau. Jacob dressed in his brother's robes, with goat skins on his hands and the smooth nape of his neck, to make him hairy like his brother. Deceived by Jacob's smell and feel, lulled by the savory dish Rebecca made for him, Isaac gave the blessing.

This ancient story of deception, or the equally old one of the Trojan horse, has much to do with the way pharmaceuticals work, and the strategy of drug design.

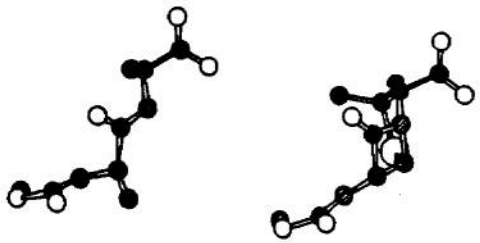
In 1928 Alexander Fleming observed that bacterial growth is inhibited by a mold. Perhaps one should have come to that discovery earlier, for there was persistent folklore of molds that combated infection. It took a decade to isolate the active agent, the molecule of penicillin. This first general antibiotic came into use in the nineteen-forties, saving millions, literally millions of lives. Many of us of a certain age remember Orson Welles and the zither theme in Carol Reed and Graham Greene's *The Third Man*. But we have probably forgotten what Welles's nasty Harry Lime made a fortune peddling. It was penicillin. In his novelistic retelling of the screenplay of the movie, Greene quotes prices of up to 70 pounds a phial on the black market. In the preface to the book he tells the story of a surgeon in London who took two friends to see the film. Surprised to see them subdued by this magnificent "fairy tale," he learned that they themselves sold penicillin illegally while in Vienna after the war.

It wasn't until twenty-five years later that we learned *how* the

drug routs the microbe hordes. When one follows under a microscope a bacterium attacked by penicillin one sees it swell and explode. But the drug is not a mortar shell; it does its desired violence by deception, interfering with the bacteria's production of its own cell wall. That wall is a gigantic net bag, a *peptidoglycan*, a molecule that is a mix between sugars and proteins. It is continuously manufactured in the bacterium by a ganged series of small chemical factories, enzymes. Each enzyme does some specific task. The sugar chain is first assembled, and then, in a separate, also "enzyme-catalyzed" step, the peptide cross-links are put in, forming the two-dimensional extended architecture of the fortress-like cell wall. Here is a schematic of that last stage of bacterial home construction:



It is with this last stitching-up enzyme that penicillin interferes. It does so by lethal subterfuge. Penicillin resembles in size and shape the chemical piece (it's called D-Ala-D-Ala-peptide) the enzyme needs as the last stitch or cross-link to sew into place. Below is a representation of a molecular model of the true soldier (A) and the impostor (B):



A = part of D-Ala-D-Ala peptide

B = penicillin

The enzyme is fooled by the penicillin's camouflage fatigues; it welcomes the invading drug into its ranks, guides it to the "active site," where the chemistry takes place. But penicillin is *not* D-Ala-D-Ala-peptide. It is a reactive molecule in its own right. Once inside the enemy lines at the active site, it forms a strong bond to the bacterial enzyme, inactivating it, making it incapable of doing what it should be doing. The foe is disarmed. The bacteria's defective cell-wall armor cannot resist, the pressure in the cell grows, the bacterium swells, explodes.

The antibiotic weaponry worked splendidly for a while, ruining the microbe defense system. However, doctors soon noted an increased resistance to penicillin. There evolved strains of bacteria producing an enzyme (penicillinase) that decimated the invader before it reached the cell-wall building factories. Chemists countered by modifying the battle plan. First, they tried other weapons, not worrying why the ones they used earlier just failed. So from a sewage outlet in Sardinia came the *cephalosporins*. These got us through a few bad years, to be followed by a host of variations in penicillin's molecular architecture, tricky chemical thrusts and cuts. In 1976, after this aggressive tinkering had played itself out, we came up with a different strategy. Chemists found another extract from molds, clavulanic acid, which, once again using molecular mimicry, is taken up, now by penicillinase. It's called a penicillinase inhibitor. The mixture of an improved penicillin and a penicillinase inhibitor, called in one popular preparation "Augmentin", is the latest effective antibiotic weapon in a molecular cat-and-mouse struggle. A struggle unlikely to end.

An interesting point to reflect on is that a knowledge of how penicillin works was *not* necessary for its use. Heaven knows we use many things in this world without understanding them in detail. But once something goes wrong, in this case that a previously effective drug loses potency, then understanding (or rather lack of it) all of a sudden matters. It's hard to fix something when it breaks down, or to improve it, without really being acquainted with its innards.

Viruses are more difficult to defeat on the body's battlefield than bacteria. They're incredibly efficient packets of almost pure information, genetic material, RNA or DNA, encased in a simple protein coat. Once inside the cell, they commandeer the normal molecule-making apparatus of the cell—those enzymes I mentioned—with new marching orders: "Make more of *me*." That diversion of the