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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

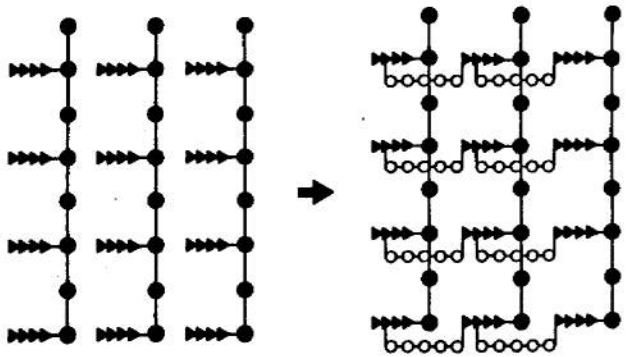
Roald Hoffmann begins: Isaac grew old and dim of sight. He wanted to impart the paternal blessing to the first-born of his twin sons, Esau. Jacob and his mother Rebecca connived to fool Isaac and cheat Esau. Jacob dressed in his brother's robes, with goat skins on his hands and the smooth nape of his 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.

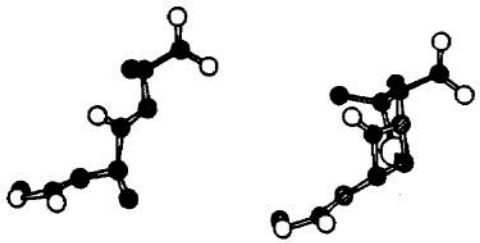
In 1928 Alexander Fleming observed that bacterial growth is inhibited by a mold. Perhaps one should have come to that discovery earlier, for there was persistent folklore of molds that combated infection. It took a decade to isolate the active agent, the molecule of penicillin. This first general antibiotic 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

cell's normal energy and chemistry, as well as the mechanics of getting the new generation of viruses out, annihilates the cell.

It's not easy to craft a strategy against an invader that uses the cells' normal processes. Gertrude Elion and her collaborators entered the fray with one, the drug acyclovir. The molecule is innocuous by itself, but in the presence of the virus and the chemical machinery viral infection sets into motion, acyclovir is converted to a compound that resembles, but is not identical to, one of the four nucleic acid "bases," the building blocks of DNA. That acyclovir "metabolite," as it is called, competes with the normal DNA building block, and is incorporated into the viral DNA. But then its little differences come into play. It turns traitor and it effectively stops further DNA synthesis, stops viral replication. Uninfected cells are not affected, since conversion of acyclovir to its active form required the virus itself.

Acyclovir, one of the first antivirals, took more than a decade to develop. And it is an effective weapon in only one theatre of this war, against a small subset of herpes-related viruses. But the lesson of strategy is more important than the drug itself; it is being applied in other skirmishes.

The tales of molecular mimicry told here are instructive in damping one human reaction to the richness and wonders of the natural world. Surely there had to be a Maker to think of those marvelous mechanisms, the intricacies of cell-wall barricades, the microscopic factories that make them, the beauty of insect wings (more well-documented biological mimicry is going on there!). But it's clear, following François Jacob, that evolution (a mechanism for making small chemical and biological changes, a selection process, lots of time to run experiments) is a tinkerer, banging into shape, with minimal change, anything that works. Molecular mimicry in drug design probes the insufficiencies of the wonderfully complicated *ad hoc* solutions that organisms inimical to us have come up with. Give them time, and they will evolve a counter-gambit.

What is also interesting is my seeming inability to discuss what transpires in drug design without the metaphor of struggle, without the anthropomorphic language of battle, or contest, or of deception. You could try to set it up in neutered language, but I think you would lose thereby not only the "color"—let that go. You would also fail to evoke, I claim, in the souls of the drug designers, the creative

urge, the motive forces that keep them going over a decade of routine and drudgery.

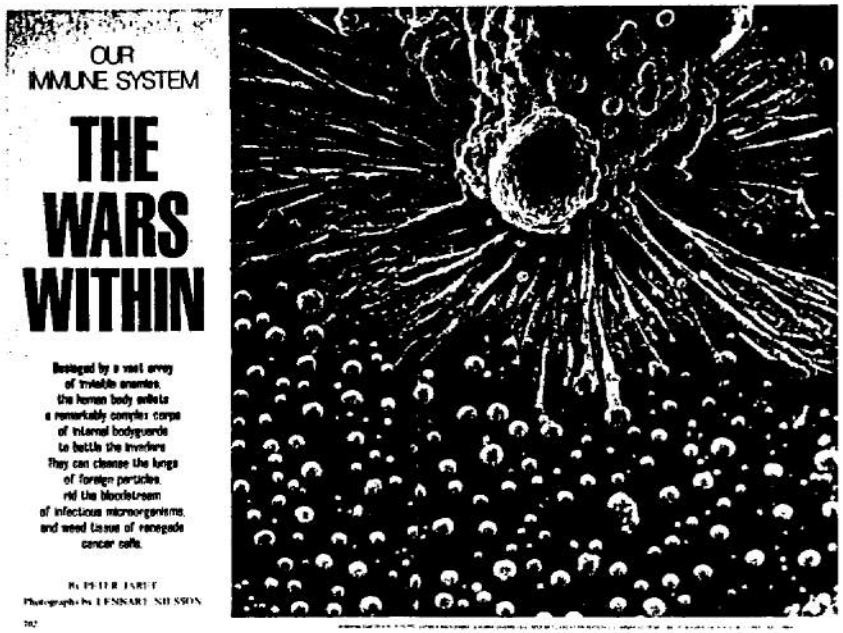
To which Shira Leibowitz replies: You claim, Professor Hoffmann, that we are unable to "discuss what transpires in drug design without the metaphor of struggle . . . battle, contest . . ." As a chemist with two books of published poetry to your name, you should have more imagination.

The problem of metaphors is not a marginal one in science. What facet of themselves are chemists and immunologists presenting to the public when popular expositions of their science read like World War II scenarios? Your lethal lexicon, Professor Hoffmann, includes such phrases as: "molds that combated infections," "the drug routs the microbe hordes," "fortress-like cell wall," "lethal subterfuge," "fooled by the penicillin's camouflage fatigues," "welcomes the invading drug to its ranks," "inside enemy lines," "cell-wall armor," "decimated the invader," "battle plan," "commandeer . . . with new marching orders," "annihilates the cell," "entered the fray," "acyclovir . . . turns traitor . . . and it is an effective weapon in only one theatre of this war."

To be sure, this martial terminology is not your idiosyncrasy, Roald, (although you employ it with gusto); it is the standard arsenal of professional and popular immunology. In the June 1986 *National Geographic* in addition to the astounding visual feast of Lennart Nilsson's photographs we were treated to a no less astounding verbal carnage. Peter Jaret's text is riddled with idiomatic shrapnel, from the title and first sentences ("Our Immune System: The Wars Within," "Every minute of every day wars rage within our bodies. The combatants are too tiny to see") up to the very last phrase ("In the battle against disease, such hope may be the strongest weapon we have").

Time magazine is even more explicit on a 1988 cover about immunology. For readers who lack the imagination to conjure up "The Battle Inside Your Body," a picture is provided inside of cells in a boxing match; it is captioned "The White-Cell Wonder Vs. the Vicious Virus." Outdoing *National Geographic*, the *Time* lexiconic body-count reaches twenty deadly terms in its first column of copy alone.

An article on a new drug, niclosamide, in *Science*, a supposedly more serious magazine, can't pass up the martial language. It is



First page of *National Geographic* article, June 1986, p. 702. Text by Peter Jaret, photograph by Lennart Nilsson.

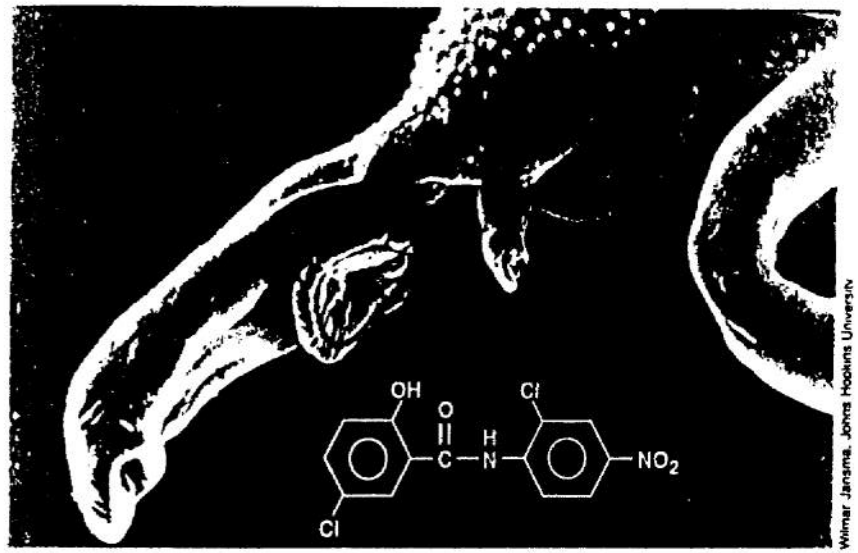
titled "New Weapon in the War Against Schistosomiasis", and the sexy picture has a legend that begins "Public enemy, public weapon."

Aggressive metaphors in language not only *reflect* the quality of our life, but *affect* it as well. Let us turn to our writers for a diagnosis. The Israeli novelist Amos Oz has articulated one aspect of this problem:

> Contrary to the sentimental, romantic cliché, poets do not handle words as a lover handles bouquets. They treat words the way a bacteriologist treats germs. As a result of their work and their intimate, microscopic contact with language and its implications, they are sometimes able to detect disease or the threat of an epidemic before others do. Here is a small example. For several years, we have been able to hear, in colloquial Hebrew, that the love life of the Israeli male is conducted somewhat like this: He meets a bombshell, puts her into a state of preparedness, and then lifts her off on a missile. Unless, that is, he gets torpedoed along the way.

New Weapon in the War Against Schistosomiasis

Research by the U.S. Army has turned up a compound that prevents infection by the schistosomiasis parasite



Excerpt from *Science*, 246, 1242 (1989), text by J. Cherfas, photograph by W. Jansma. Copyright 1989 by AAAS.

> When love uses language like this, it is a sign that the disease of violence has already filtered into the innermost tissues of our being. A sign that the war has stormed in and conquered even our beds. One who thinks and speaks of his beloved in such language . . . Better, perhaps, to leave this sentence unfinished. I want to emphasize that I am not talking about corruption of the language, but about blindness. Our language and, with it, our world are clouded by thick smoke.

Professor Hoffmann, you would like our science, also, to be smothered in battlefield smoke. Contrary to your contention, it does not have to be that way.

For a start let's discard your Biblical metaphor of two warring brothers, Jacob and Esau, in favor of two cooperative sisters, Rachel and Leah. In Genesis the two sisters are bridal candidates for Jacob, who eventually wins the hands of both sisters, through an episode involving mimicry and camouflage. The story begins in Chapter 29 with what may be the first recorded case in history of love at first sight, or at least kiss at first sight.

> . . . Jacob saw Rachel, the daughter of his uncle Laban . . . Then Jacob kissed Rachel, and broke into tears . . . Now Laban had two daughters; the name of the older one was Leah, and the name of the younger was Rachel . . . Jacob loved Rachel; so he answered 'I will serve you seven years for your younger daughter Rachel.' . . . So Jacob served seven years for Rachel and they seemed to him but a few days because of his love for her. Then Jacob said to Laban, 'Give me my wife, for my time is fulfilled, that I may consort with her.' . . . When evening came, he [Laban] took his daughter Leah and brought her to him; and he cohabited with her . . . When morning came, there was Leah! So he said to Laban, 'What is this you have done to me? I was in your service for Rachel! Why did you deceive me?' Laban said, 'It is not the practice in our place to marry off the younger before the older. Wait until the bridal week of this one is over, and we will give you that one, too, provided you serve me another seven years.' Jacob did so . . . indeed he loved Rachel more than Leah.

How could Leah have substituted undetected for the beloved Rachel under the bridal canopy and in the nuptial bed? Jewish legend (the Midrash) fills in the lacuna in this tale of mimicry. It tells the following story. Rachel had warned Jacob that her father might try to substitute Leah in her stead, so Jacob taught Rachel secret signs by which he would know her (one commentator says the signs consisted in Rachel touching Jacob's right toe, thumb, and ear lobe.) Jacob took another precaution: he warned Laban not to change his older daughter's name to Rachel in order to fob Leah off on him.

The night of the wedding, wily Laban extinguished all the candles and brought in Leah, dressed as the bride. Jacob, prepared for deceit, asked the bride for the pre-arranged signs. She responded satisfactorily. How was this possible? When Leah was about to be

Mortitz Oppenheim (1800–1882), *The Wedding*, 1861
Oil on Canvas
The Israel Museum, Jerusalem

presented as the bride, Rachel did not want to expose her sister to public shame and cooperated in the ruse. She revealed to her sister the secret signs. She even hid in the room where the couple were staying and, like a ventriloquist, answered Jacob's precautionary questions, so that Leah's voice would not reveal the truth to him. Jacob did not discover the fraud until the next morning. "How could you pretend to be Rachel and answer me when I called you her name?" Jacob angrily demanded of Leah. She replied, "I am your student—I learned from you how to do it. Didn't you come to your father, Isaac, masquerading as Esau? I only followed in your footsteps."

Incidentally, this episode is commemorated today at Jewish weddings in the custom called "bedecken." Before the ceremony, the groom personally checks that the unveiled bride is the intended and not a substitute. Then he veils her by himself. The veil must be sheer enough so two witnesses can vouch for the bride's identity. Then the groom circles the bride seven times with special candles (or the bride the groom, depending on the custom of the community) for final verification. All this to prevent another Leah/Rachel switch. In Moritz Oppenheim's classic painting the bride appears unveiled . . . just to be sure.

This ancient story of the Leah/Rachel deception has much more to do with the molecular mimicry of pharmaceuticals at work than do the Jacob/Esau or Trojan horse subterfuges.

Having recast the molecular drama as a romance, we can still do away with the undesirable cells, for as the current poet laureate of Israel, Haim Guri, has observed in his poem "Visitation"—"You can die from love./ Not only from nefarious diseases, from bullets, from concentration camps and from malnutrition." An earlier poet laureate of Israel, King Solomon, similarly noted in his Song of Songs that "Love is as strong as death . . . the flashes thereof are flashes of fire . . ." Or, as Ben Jonson wrote,

> Though I am young, and cannot tell
> Either what Death or Love is well,
> Yet I have heard they both bear darts,
> And both do aim at human hearts;
> And then again I have been told
> Love wounds with heat, as Death with cold;
> So that I fear they do but bring
> Extremes to touch, and mean one thing.

> As in a ruin, we it call
> One thing to be blown up or fall;
> Or to our end like way may have,
> By a flash of lightning or a wave:
> So Love's inflamèd shaft or brand
> May kill as soon as Death's cold hand;
> Except Love's fires the virtue have
> To fright the frost out of the grave.

Let us see how this can work in immunology. Instead of "NK cells" (natural killer cells), the researchers will be dealing with NL cells (natural lover cells). "Surveillance" mechanisms will be replaced by molecular courtship and flirtation; the unwanted cells can be hugged and kissed to death. As Shakespeare observes after Romeo and Juliet die, "heaven finds means to kill . . . with love." The Elizabethan poets had it right in their common locution of death for sexual union.

Away with the neutered T and B cells (named uninspiringly after the Thymus and Bursa organs). How much more appealing to deal with L cells (after Leah) which mimic R cells (Rachel cells), snuggling up to the unsuspecting bacteria. Immunological terror can be turned into erotic trysts, and battles into orgies. As Laban set up his daughter for his duplicity, so drug designers craft molecules that deceive. Could Rachel passing secret information to Leah have an analogy to the esoteric byways of RNA-DNA information transfer?

Scientists can be imaginative. A gene responsible for a certain mutation in the eye of the fruit fly *Drosophila* is called *sevenless*. The mutation leads to loss of a photoreceptor in the course of development of the fly's retina. Why? Because a protein, named by Gerald Rubin, *bride of sevenless*, is unfulfilled.

In addition to Biblical legend and Elizabethan literature, we can turn to music and art for inspiration in finding metaphors for science. Richard Wagner's *Liebestod* scene, where Tristan and Isolde sing of their readiness for love/death comes to mind, with its compelling ecstasy repeated in the orchestra and in the voices. Tristan sings "Thus we might die, undivided, one forever without end . . . embraced namelessly in love." And a little later in the same scene, both proclaim, "Now banish fear, sweet death, ardently desired death in love!" Now here is a way for bacteria to go!

In a different spirit, love and death are depicted by Delacroix in his painting of the "Death of Sardanapalus", which portrays the

ruler's demise surrounded by his harem. The picture was inspired, as was a cantata by Berlioz, by an influential play by Byron about the Assyrian king whose mistress shows her devotion by joining him in a pyre of death. If love could inspire Byron, Delacroix and Berlioz, could it not inspire scientists as well?

You, Roald, limit us to only two choices: battle terminology or neutered language. But there is a third alternative. Certainly Venus would be as successful as Mars in inspiring those hard-working drug designers.

Roald Hoffmann: You have a point, Shira. So let me try it again.

We take up the penicillin story at the stage of the bacteria's net-bag-cell-wall-sewing-up enzyme. The enzyme holds on to some molecules less well than others. Obviously it favors the D-Ala-D-Ala-peptide, which has evolved and is produced in the bacteria for that

Eugène Delacroix, *La Morte de Sardanaple*
Musée de Louvre
Photo courtesy of the Réunion des Musées Nationaux

purpose. Penicillin comes along; this alluring stranger wasn't around when the enzyme evolved—it happens to *bind* better than the intended peptide. Moreover penicillin is chemically reactive in ways that the D-Ala-D-Ala-peptide isn't. The setting at the heart of the enzyme—binding, disposition of reactive functionalities, the local acidity—is suitable. It is inevitable that penicillin and the enzyme couple; the chemistry is right. Now more or less permanently bound, the enzyme-penicillin duo is physically unable to do what the enzyme was supposed to with its original substrate, the peptide, which was to make an essential piece of cellular clothing. That cell wall is not impenetrable armor, it's a coat of many colors, with all kinds of ingeniously crafted openings and passages for molecular commerce. The organism dies, for love, if you like.

But in that bacterium there are other molecules that bind penicillin to a certain degree, not only that critical sewing-up enzyme. Some do it poorly, some do it well. One bacterial molecule, penicillinase, has a particularly strong affinity for penicillin. There's a natural variation in the amount of penicillinase. Those individual microbes that possess by chance or mutation more penicillinase have an advantage, for they can divert more penicillin from the initial cell-wall building enzyme. With time, strains of bacteria with enhanced penicillinase activity evolve, playing on that natural variation.

Our wonderful chance discovery, a drug interfering with an enzyme, no longer works. The zing is out of the romance. But now the binding strategy is pretty clear; the cast of characters and molecular entanglements grows as in a Renaissance comedy. We concoct a new molecule to seduce penicillinase.

Could it be that the appropriate metaphor for the drug designer is not that of a general, but a playwright? Or a matchmaker, in a game of elective affinities, to borrow a phrase from Goethe and eighteenth century chemistry? The game is life.

I tried to tell the story plainly. But I could not avoid the implication or explicit use of metaphor, now that of bonding or affinity, with its inevitable shading over to affection and love. Just a touch more and I would be past innuendo and into broad sexual comedy.

I think your argument is still overstretched; as a prominent chemist who has worked on penicillin remarked, "It's hard to think of love when the intent is slaughter." On the other hand a friend of

ours, an Israeli immunologist teaching a summer course to Palestinian physicians from Gaza, remembers that he suddenly felt self-conscious about the stock language of his field, and started to cast around for alternatives.

Thomas Pynchon writes: "The act of metaphor then was a thrust at truth and a lie, depending where you were: inside safe, or outside lost." What is it that makes it impossible to describe a series of events without stirring up metaphor, be it that of love or war, in our minds? The same thing, friends, that makes it possible to think up, and portray that wondrous series of molecular events at all. Or to tell the story of Jacob and Esau, of Jacob and Leah and Rachel. Just words, those of a language, any *human* language.

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