New 'design rules' yield novel drugs

With physicians' predilection these days for treating common infections with antibiotic drugs, medications such as tetracycline and erythromycin have become familiar to the average U.S. family.

Few people realize, however, that these drugs belong to a large family of naturally occurring compounds called polyketides. This class of chemicals has proved such an abundant source of potent drugs that scientists have longed for an organized system by which to "rationally design" new variations of known drug themes.

Other useful members of the family include such medicines as monensin and ivermectin, both fighters of parasites; FK506, a suppressor of the immune system; and doxorubicin, a killer of cancer cells.

Now, Robert McDaniel, a chemical engineer at Stanford University, and his colleagues have developed such a system. They describe in the June 15 NATURE a set of "design rules" that they have developed to create new kinds of polyketides from bacteria. To demonstrate the efficacy of their new system, the chemists successfully used the rules to predict, design, and synthesize two novel polyketide molecules.

"These studies, which began in a largely empirical mode," the scientists say, "have now reached the point of revealing strategies for the rational design of novel aromatic polyketides, as we show here by the production 'to order' of the two new polyketides SEK43 and SEK26."

Bacteria of the genus *Streptomyces* harbor a group of enzymes, called polyketide synthases, that manufacture polyketides. The new design rules essentially enable scientists to genetically engineer novel enzymes that synthesize the desired polyketide variations.

The rules cover such details as the construction of molecular rings and chains on the enzymes, which then lead to polyketides with specific molecular features.

"As a family of molecules, the polyketides have an almost unsurpassed track record of supplying useful drugs," says Stanford chemical engineer Chaitan Khosla, a coauthor of the report. "But so far, finding those compounds has been largely hit or miss."

"The significance of our approach is that it gives us a practical set of tools for making novel 'natural' polyketide compounds," he says.

Ironically, he calls the polyketide variants "unnatural" natural compounds.

With the explosive growth of synthetic chemistry in the pharmaceutical industry, more than 10,000 polyketides have been discovered, Khosla estimates. In recent years, however, the hit rate of finding medicinally useful compounds has dropped.

"Either we're exhausting the natural compounds," he says, "or we're not looking in the right places."

Yet based on the recent findings, Khosla and his colleagues now believe that the known medicines derived from this class of agents represent "only the tip of the iceberg."

"We now think there are vast numbers of potentially useful polyketides out there waiting to be discovered," Khosla says.

From a scientific point of view, the process of genetically engineering bacteria to produce mutant enzymes, then analyzing the products of those enzymes "has taught us an incredible amount about how these molecules work," Khosla says.

Scientists have likened this method of drug discovery and synthesis to "making chocolates with the wrapper on," Khosla says. "We tinker with enzymes, then look at the reaction product.

"But in some sense we don't know what we have until the wrapper comes off." —*R. Lipkin*

Coming: Drug therapy for chocoholics?

Few foods top chocolate's popularity. The 2.86 billion pounds of this candy shipped annually in the United States contribute to an average per capita consumption of more than 11 pounds.

New data now suggest that in especially vulnerable people, the ready availability of this and other sweet, fatty foods can fuel a binge-eating addiction. But drugs that block naturally produced opiates—heroinlike chemicals in the brain—can help binge eaters break their periodic compulsion to overeat, a pair of new studies indicates.

Nutritionist Adam Drewnowski of the University of Michigan School of Public Health in Ann Arbor and his coworkers studied 16 obese women and 25 women of normal weight. Ten women in each group met the criteria for either bulimia or a "binge-eating disorder" listed in the latest *Diagnostic and Statistical Manual of Mental Disorders*.

On three occasions, the women rated their preference for foods in four categories: those low in fat and sugar (including popcorn and pretzels), low in fat but high in sugar (including jelly beans), high in fat but low in sugar (such as potato chips and cream cheese), and high in both fat and sugar (chocolate in candy and cookie form).

Each woman then received at random a 2.5-hour-long infusion of naloxone (which blocks the action of the brain's natural opiates), salt water, or butorphanol (a drug that can both potentiate and block opiates). An hour into the treatment, researchers again assessed food preferences, then gave each woman a tray containing personally identified favorites from each category, with instructions to eat all they wanted.

Though naloxone diminished each woman's preference for sweet and, especially, fatty foods, it did not affect perceptions of sweetness or fattiness. However, in women diagnosed as binge eaters—whether obese or lean—that change in preference also translated into a change in eating choices, the Michigan researchers report in the June AMERICAN JOURNAL OF CLINICAL NUTRITION.

Obese binge eaters ate fewer calories during the naloxone treatment, and all binge eaters reduced their consumption of sweet, fatty fare, compared to the two other treatments. Lean and obese nonbinge eaters, by contrast, ate the same type and amount of food in all three sittings.

"Our study is the first psychobiological validation that there is something special about binge eaters, whether lean or obese," Drewnowski told SCIENCE NEWS. Only the binge eaters changed eating patterns in response to opiate blocking. Because all of the study's sweet, fatty foods contained chocolate, he notes, one can't tell whether chocolate is unusually addictive. But, he adds, it is the food most craved by women.

Pharmacologist Mary Ann Marrazzi says this study confirms what her team at Wayne State University in Detroit saw in a 6-week trial with 19 bulimic and anorexic binge eaters. In the next INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, her team will report that daily treatment with another brain-opiate blocker reduced the number and intensity of binges in all but one person.

"It interrupts their addictive cycle," Marrazzi says, "so that psychotherapy can be more effective." —*J. Raloff*