Smuggling drugs across brain border

Nicholas Bodor is running drugs — across the brain's blockade. He has found a way to chemically modify drugs so that they will more easily penetrate the brain's protective barrier.

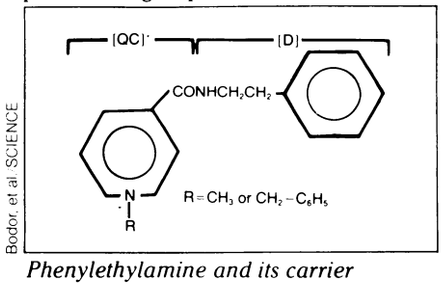
That barrier, called the blood-brain barrier (BBB), consists of tightly joined lipoidal (fatty) cells that form the blood-carrying capillaries to the brain. The barrier's purpose, explains Bodor, of the University of Florida, "is to prevent all kinds of chemicals from easily entering the brain." And the barrier works well. It works so well, in fact, that it also prevents useful therapeutic drugs from easily entering the brain.

Now, however, Bodor and colleagues have developed a technique that enables drugs to penetrate the barrier. The drug-running scheme, reported in the Dec. 18 SCIENCE, is a method that Bodor expects will be applicable to a "very large number of drugs."

According to the scheme, a drug [D] is attached to a quaternary carrier $[QC]^+$ — so called because it has a nitrogen atom bonded to four constituents, giving the carrier a positive (+) charge. Then, to make the resulting complex $[D\text{-}QC]^+$ more like the lipoidal cells that compose the BBB so that it can more easily slip through that barrier, one more chemical modification is performed — reduction. In this case, reduction involves adding hydrogen to the carrier portion of the complex, transforming it into the desired neutral, lipoidal form [D-QCH]. At this point, the drug-carrier complex would be administered to the patient.

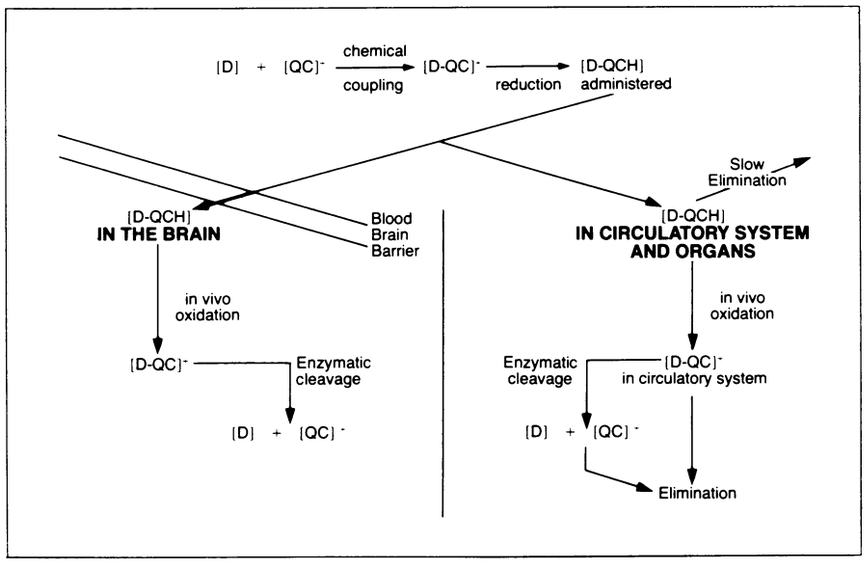
In the body, some of this chemical complex would run the brain's blockade. Inside the brain, one of the body's numerous oxidizing systems, such as $NAD^+ \rightleftharpoons NADH$, would grab the hydrogen from the [D-QCH]. The complex then would be back in its nonlipoidal, charged form — the form that cannot penetrate the barrier. As a result, the complex would be trapped where it is needed. Next, "Enzymatic cleavage of the $[D\text{-}QC]^+$ that is locked in the brain [would] result in sustained delivery of the drug species [D]," Bodor and colleagues report.

Bodor first tried this scheme with a drug used to treat poisoning by organophosphates — a group of chemicals used in a variety of applications including pesticides. That drug, 2-PAM, easily penetrated the BBB of mice in its reduced form and was oxidized to its active form inside the brain. This Bodor reported in the Oct. 10, 1975 SCIENCE.



Bodor, et al./SCIENCE

Phenylethylamine and its carrier



After Bodor, et al./SCIENCE

The drug would be locked in the brain and easily eliminated from the rest of the body.

In the more recent work — two rat experiments — Bodor and colleagues demonstrated that the same reduction-oxidation technique is a general method that can be used to deliver many types of drugs to the brain. In one experiment, the researcher used the method to deliver phenylethylamine — a chemical chosen as a model because it is structurally similar to compounds such as dopamine, whose chemical precursor, L-dopa, is used to treat Parkinson's disease. In another experiment, Bodor and colleagues used their technique to deliver berberine — a drug that shows anticancer activity. In this study, the researchers found nearly 50 times more reduced berberine than unmodified berberine in the rat brain.

Currently, Bodor and colleagues are investigating whether their drug delivery method also is effective for a particular contraceptive steroid and small peptides, such as those used as analgesics.

— *L. Garmon*

America's first test-tube baby

Besides the English language, what do England, Australia and the United States have in common? The answer is the birth of "test-tube" babies, or children fertilized in laboratory dishes and reimplanted into their mothers' wombs to grow until the time of birth. England's first such infant was born three years ago, Australia's subsequently and the United States' first one this week — at the Norfolk General Hospital in Norfolk, Va. The child is Elizabeth Jordan Carr, and the parents Judith and Roger Carr of Westminster, Mass. The physicians who made the birth possible were Howard and Georgeanna Jones.

The Carrs were among the 600,000 American couples who are unable to have children because the wives have damaged or missing Fallopian tubes through which a fertilized egg normally reaches the womb to develop. So they sought to have a child via laboratory fertilization and embryo transfer at the United States' first clinic trying the method. It was at the Eastern Virginia Medical School in Norfolk and headed by the Joneses. The Joneses gave Judith Carr fertility-inducing hormones to make her ovulate at a fixed time, removed a fertilized egg from her, and placed it, along with sperm from her husband, in a shallow dish. One of the sperm fertilized the egg, and when the egg had become an embryo, it was inserted into Judith Carr's womb, where it attached itself, developed into a fetus and grew normally until it was born this week.

Although "test-tube" births are still extraordinary medical events, they are becoming more common as scientists such as the Joneses hone their techniques and as more scientists attempt to apply the methods. For instance, the world's pioneers in test-tube midwifery — Robert Edwards and Patrick Steptoe of England — delivered their sixth such baby in November, and dozens of women in England, Australia and the United States are purportedly now pregnant with fetuses fertilized in laboratory dishes. So what does the future hold for this form of human reproduction? As an editorial in the Dec. 5 LANCET points out, "Certainly it will not supplant established methods [of infertility management].... It is not hard, however, to envisage the day when *in vitro* fertilization and embryo transfer is simple and reproducible and complements these methods...."

— *J.A. Treichel*