Tossed in Translation

FIFTY YEARS AGO, ACADEMIC RESEARCHERS RARELY found themselves embroiled in the ethics of translating their findings into useful drugs. They didn't worry that acceptance of consulting fees, industrial grants, or patent royalties might jeopardize their scientific objectivity or credibility. Many scientists of my generation, though, have decided to weather those risks; indeed, some investigators at the National Institutes of Health (NIH) are considering moving to institutions with less restrictive policies on commercial relationships. Others suspect that society suffers when distinctions between publicly supported and commercial investigations blur. One such skeptic was my mentor, Julius Axelrod.

Julie loved science. Weeks before he died last year at the age of 92 he was still visiting his old NIH laboratory and helping younger investigators design the simple, elegant experiments that were his trademark. Such experiments allowed him to make major discoveries about how the brain works, such as the uptake process, which terminates the actions of serotonin and other neurotransmitters. Another was a pain-relieving chemical, acetaminophen, now known commercially as Tylenol; when he published that finding in 1948 he neither thought to have it patented nor manifested an interest in participating in its development as a drug. Julie hoped, of course, that his discoveries would translate into new medicines. But to him, and to most of his generation, drug development was something pharmaceutical companies did, not research scientists.

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My expectations differed. By the time I joined Julie's lab in 1962 as a research fellow, neuroscientists were learning enough about brain transmitters to understand how certain drugs worked. I decided to use my medical training both to discover information about the brain and to apply that knowledge to treating neurological and psychiatric diseases. I formulated a three-stage strategy. First, using laboratory animals, I would try to find a previously unknown biochemical process in the brain—measuring blood levels of melatonin, for example, or identifying the amino acids that control serotonin production. Then I'd determine whether the same process operates in healthy human subjects. Finally I'd draw on my medical background to identify diseases that might respond to any drugs that could affect the process I'd discovered.

Shortly after I arrived at MIT in 1968, my laboratory found that surprisingly low doses of tryptophan could increase production of the neurotransmitter serotonin in the rat's brain. We described our finding in leading journals and confidently awaited its application to serotonin-associated disorders, such as stress-related insomnia. It was indeed applied; by the late 1970s the annual market for tryptophan supplements had reached $300 million. The amino acid, however, was being misused: Not only were suppliers selling it in doses that varied over a 20-fold range, but they were also failing to provide accurate advice about its best administration, such as not taking it with a glass of protein-rich milk.

Tragically, in 1989, a new commercial preparation of tryptophan, generated by a newly engineered microorganism, killed several dozen Americans because the microorganism also produced two previously unknown toxins. None of these people would have died had the developers carried out standard Phase I safety testing on the new commercial preparation. I worried that I had erred by not staying involved in the process of tryptophan's transition to a drug. But I also couldn't think of any way I might have compelled the companies selling tryptophan to solicit my advice.

In 1980 the power of university scientists to affect the fate of their discoveries reached a watershed with passage of the Bayh-Dole Act. It had not escaped Congress's notice that troublingly few of the federally funded basic-science discoveries taking place at universities were being translated into useful treatments. The legislature concluded that this situation might improve if universities were given the right to patent those discoveries, to license the patents to companies that would develop them expeditiously, and to maintain some association with the development process.

MIT—and, ultimately, most universities—established a technology licensing office to implement these processes. Soon thereafter the director of MIT's office informed me that if I ever wanted to see my discoveries become medications, I needed to work with his office to help MIT patent them and to find licensees that would develop them. Without patent protection,

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he explained, pharmaceutical companies had no incentive to undertake the risky business of developing a new drug if a competitor could market the same drug, a short time later, after having covered none of its development costs.

Many of my laboratory's discoveries have since been patented—always by MIT—and then licensed, and a few have become useful therapeutic products. But I've had to participate in all phases of this translation process and to learn about fields—such as patent law and drug regulation—that never concerned Julie's generation. And I've had to confront, almost daily, complex ethical issues that have arisen from my—and my university's—receipt of corporate funds, provided as patent royalties, research grants, or consulting fees.

Consider, for example, melatonin. In the 1960s, Julie and I had shown that rat pineal glands produce the hormone melatonin only when the animals are in the dark. In 1975 my MIT colleague Harry Lynch and I discovered that blood melatonin levels in people are at least ten times higher at night than during the day. My laboratory confirmed the connection between melatonin and sleep, first by showing in 1993 that it promoted sleep onset, then in 2001 that it enabled melatonin-deficient, older people to stay asleep. The correct melatonin dose—0.3 mg—turned out to be just the amount needed to raise blood melatonin levels to what they normally are, at nighttime, in healthy young adults.

MIT patented this use of melatonin, and I expected many to benefit, especially elderly people who tend to awaken during the night. But then major patent and regulatory problems arose: because the correct dose of melatonin was low, MIT elected to patent only doses up to 1.0 mg, believing that the Food and Drug Administration (FDA) would eventually approve melatonin as a drug and limit its use to the maximally effective 0.3 mg dose.

But the FDA decided not to treat melatonin as a drug; rather, it allowed the hormone to be marketed as a dietary supplement, which meant the dosage would remain unregulated. This allowed companies to sell it at high doses to circumvent the MIT patent. Such megadoses quickly rendered the melatonin ineffective: when the brain is repeatedly bombarded with excessively large amounts of a hormone like melatonin, it stops responding because the hormone's receptors become downregulated. Thus, many of the people who might have benefited most from melatonin's use lost its effect after a few days and then stopped taking it.

Only in the past year have companies finally started to sell melatonin at the correct dose. Now MIT will receive royalties—and I, as the inventor who created the intellectual property, will receive about 30 percent of these. And therein lies a potential ethical problem: Could someone argue that I recommended that people buy the low dosage because I receive royalties from those sales? Money wasn't my motivation, but I believe I have a duty to inform people about my potential conflict of interest.

PHOTO: DAVID MCGLYNN/TAXI

This obligation to fully disclose should carry over, I believe, to all financial relationships between scientists and corporations, including consultantships, substantial lectureships, and laboratory research support. Disclosure is particularly important when the scientist's career involves addressing the public, writing review articles, or editing journals. Consumers have the right to any information that could raise questions about a scientist's objectivity—even when the scientist in question is a Julie Axelrod.

In Julie's case, of course, it's unlikely the question would ever have arisen, since his choice to steer clear of the translation process shielded him from the ethical consequences of financial involvement. It may also have cost society a few good drugs. ■

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