
Who Will Adopt The Orphan Drugs?

Louis Lasagna

LET US SUPPOSE a massive radiation leak occurs somewhere in the United States, creating an urgent need for an effective antidote for plutonium poisoning. The government has, of course, long been seeking such an antidote and comes riding to the rescue in the nick of time.

This is fiction. In the real world, not only has our government's commitment to searching for a plutonium antidote waned in recent years but a promising antidote has never been made available because of excessive regulatory demands.

There is a simple chemical relative of EDTA (a "chelating" or "leeching" agent used to treat lead poisoning) that is the most effective agent known for reducing plutonium in the body if given by intravenous injection promptly after exposure to radiation. Needless to say, health officers in the few laboratories where plutonium accidents might occur wanted to stock this drug in case of emergency. Moreover, the scientists in the company that discovered it persuaded management that it had a moral obligation to make the material available. The scientists also foresaw diagnostic utility for the drug in two other uncommon, and hence com-

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mercially unattractive, clinical situations: low-level lead intoxication and iron overload. In these instances, a single modest dose of the drug would suffice.

So far so good. But now enter the federal government in the form of the Food and Drug Administration (FDA).

The FDA demanded long-term toxicity tests at three different dose levels in each of two animal species before the drug could be approved (though the drug had already been given to animals in large intravenous doses daily for a month, without harm). In other words, the FDA wanted a full-scale project typical of that required to market an ordinary drug—a project of the sort that costs upwards of \$50 million

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these days. But what was involved here was a drug whose market potential was, to put it mildly, negligible. In the end, the company decided that while it was willing to manufacture a "public service" drug on which it would lose money, it did not feel obliged to fight for the privilege. The project was dropped.

One might think this to be an isolated case. Not so. It is merely another in a long series of "orphan drug" cases—where an agent with exciting potential for treating human disease is blocked through lack of interest on the part of the people and institutions whose commitment is necessary for bringing it to market. The reasons for "orphanization" are many. But one point is central to them all—*orphan drugs* do not fit the mold in which the FDA's usual regulatory process is cast or the mold of pharmaceutical company thought that typically goes with it.

Carnitine

Another orphan, carnitine, illustrates aspects of this problem that are in some ways quite different from those of the EDTA analogue.

In 1964, a French pharmaceutical firm (Labbaz) asked Pfizer, Incorporated, if it had any interest in the possible antihyperthyroid activity of carnitine, a naturally occurring biological substance present in most mammalian tissue, with relatively high concentrations in the heart. Pfizer asked Stephen De Felice, a young doctor working in its laboratories, to check it out clinically. To his surprise, De Felice found that three classically hyperthyroid patients, when given carnitine, became free of their symptoms within a week, with their abnormally rapid pulse rates dropping toward normal. Moreover, during the course of these experiments, one patient reported that his angina pectoris was better for the first time in years. De Felice recalled this observation later, after a thorough reading of the world literature on carnitine, and postulated that carnitine could provide needed metabolic fuel to a heart with a partially blocked blood supply. He arrived at this idea quickly enough, but it took the next thirteen years to test it successfully in humans.

First, through cardiovascular experiments in dogs, it was learned that carnitine protected the heart against coronary artery spasm or occlusion. Next, the drug was found to protect both dogs and guinea pigs against the toxic effects of diphtheria toxin and, in the case of anesthetized dogs and pigs, to stimulate heart function and to offset the cardiodepressant effects of several drugs. Also it could protect dogs against the lethal shock caused by toxins pro-

duced by bacteria. Most amazing, in some respects, was the ability of carnitine to protect animals against the severe cardiac toxicity of two powerful anticancer drugs without impairing the antitumor activity of those drugs.

Not unreasonably, De Felice expected that academic and industrial experts would be as excited as he was. But not so. The findings were almost too good to be true, and there was no precedent for this kind of drug. Furthermore, most of the data were unpublished and hence could be said not to have passed the critical scrutiny of editorial referees. The data were unpublished for a good reason—the absence of a secure patent position. One cannot patent a natural substance as such, and a "use" patent was not really sufficient in this case because of the possibility that carnitine would have numerous uses. Suppose, for example, one had a valid patent for its efficacy in heart disease and carnitine turned out to be good for headache or something else? How could one guarantee to an interested company that some johnny-come-lately competitor would not make off with the biggest market?

But De Felice was not to be denied. In 1969, having left Pfizer, he began clinical trials in Costa Rica and Yugoslavia with the aid of a modest \$15,000 grant from a German company. The initial results were disappointing. Indeed, had it not been for a single patient in shock (stemming from bacterial infection) whose blood pressure responded after carnitine, human studies might have stopped. But because of this case, two University of Wisconsin scientists recommended that carnitine be tried in coronary patients subjected to electrical stimulation of the heart. To De Felice's surprise, the study showed that carnitine allowed diseased human hearts to respond better and longer to such "atrial pacing." These conclusions were then confirmed through tests on patients in whom angina would be precipitated by exertion on a bicycle or treadmill.

Meanwhile, back at the front office, company after company either refused to support the research or dropped out after temporary involvement. Ultimately, De Felice found a sponsor in the person of Dr. Claudio Cavazza, the young and dynamic president of the Italian drug firm, Sigma-Tau. It took all of one hour for Cavazza to see the scientific and commercial promise in carnitine. Without delay, a new U.S.

company was formed to pursue marketing here, while Sigma-Tau proceeded with European sales.

The paradox is that carnitine could conceivably turn out to be one of the most important drugs of recent times. Not only is there a lot of heart disease in this world, but the drug has possibilities for everything from muscular dystrophy and cancer chemotherapy to intravenous feeding. Hardly a month goes by without a new scientific communication about this interesting material. And, best of all, it is remarkably nontoxic.

By now De Felice has spent \$60,000 of his own money on carnitine—perhaps not much as medicinal drug development costs go, but enough to discourage most solo entrepreneurs. It would be a lovely twist of fate if he were to reap handsome financial rewards from a drug rejected by thirty-two U.S. and international companies. The rejections were, to be sure, mostly understandable. Until now, carnitine has been a victim of its natural origins, which make it unpatentable, and its unorthodox and varied effects, which mean that there is no precedent for its many actions and therefore little chance for it to enjoy smooth sailing at the FDA.

Dopamine, Triethylene Tetramine, and L-5HTP

A turn of events giving De Felice large profits would not be without precedent. Dopamine, another naturally occurring substance, was investigated for years by Dr. Leon Goldberg, who first became interested in cardioactive drugs as a graduate student in 1949–1952. Later, while at the National Institutes of Health, he fortuitously discovered that dopamine had highly desirable characteristics for treating heart failure. Results from dog experiments were soon corroborated in human tests, as four critically ill patients improved on dopamine after failing to respond to digitalis and diuretics. Moreover, the experiments in man showed something that the dog experiments had not: a beneficial and unique effect on kidney blood flow. This finding, whose clinical importance is very great, suggested dopamine's use in the treatment of shock, where it again proved beneficial.

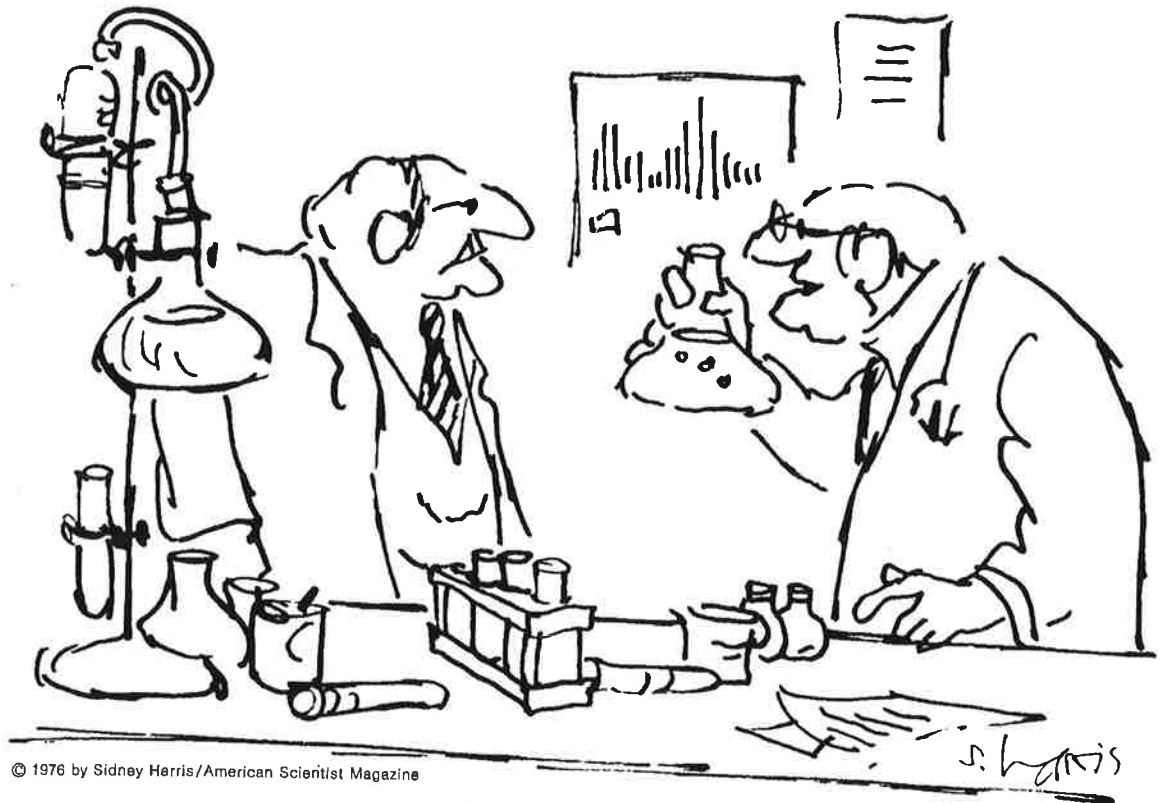
At this point, even though it was already clear from *human* studies that dopamine was at least as safe as marketed drugs for treatment

of shock, the FDA demanded animal toxicity data—which meant tests that Goldberg could not afford to carry out. So began the search for a commercial sponsor. In 1966, the total market for drugs used in treating shock was \$2.5 million. To perform the studies needed to seek approval for the marketing of a drug cost between \$2 and \$3 million at that time. Since dopamine was a natural substance and therefore unpatentable, commercial interest was limited. In addition, the raw material was expensive to make. Nevertheless, Goldberg finally found an interested sponsor in Arnar-Stone, a modest specialty drug firm located in the Midwest. After seven years of frustration, the drug was approved by the FDA in 1974, some sixteen months after filing. In 1978, annual sales of dopamine were over \$15 million. Not bad for an adopted orphan!

While the examples of carnitine and dopamine come from the cardiovascular field, orphan drugs are by no means restricted to any one area of therapeutics. The next two examples have to do with the central nervous system.

The first is triethylene tetramine, discovered by one of Britain's most distinguished neurologists, Dr. J. M. Walshe of Cambridge University. In 1950 Walshe began some experiments that ultimately led him to suggest the use of penicillamine in the treatment of patients with a rare ailment called Wilson's Disease. These patients lack the genes necessary to keep body stores of copper below the toxic level. Excess copper is deposited mostly in the liver and brain, where it leads to organ failure and death. Penicillamine has actions similar to those of EDTA, being able to leech copper from the body. In 1956 Walshe showed it to be virtually a miracle drug for sufferers from Wilson's Disease, and in short order the drug was approved.

But that was twenty-five years ago. Since then Walshe has learned that it is no longer so easy to market a drug for a rare disease. His interest in finding satisfactory treatments for Wilson's Disease had continued because penicillamine, while lifesaving, turned out to have side effects that can be lethal in those who are sensitive. In 1972 Walshe found a better and safer drug—triethylene tetramine, which works in patients who have failed on, or shown severe toxic reactions to, penicillamine. He now has



"IT MAY VERY WELL BRING ABOUT IMMORTALITY,
BUT IT WILL TAKE FOREVER TO TEST IT."

nineteen patients whose lives it has saved. This drug, like penicillamine, can be toxic, and making it in the pure form (which seems to have little toxicity) is a bit tricky. And unfortunately, no firm has come forth to sponsor it. This is not surprising, given the litigiousness of society today, the tendency for courts to hold manufacturers liable for any and all harm from drugs (especially in the United Kingdom), and the fact that triethylene tetramine is needed by only a handful of patients.

L-5-hydroxytryptophan (L-5HTP) is another neurological orphan drug. Its main proponent is Dr. Melvin van Woert, a neurologist at Mt. Sinai School of Medicine who was involved in the pioneer work that led to the use of levo-

dopa (L-dopa) in Parkinsonism. Just as L-dopa is the precursor of dopamine, a natural transmitter of impulses in the brain, so L-5HTP is a precursor of serotonin, another neurotransmitter. In the wake of L-dopa's success, van Woert began trying L-5HTP for various other neurological disorders that, like Parkinsonism, were characterized by abnormal movements of the body. He found that L-5HTP (plus an enzyme inhibitor) produced dramatic improvement with minimal side effects in patients with myoclonus, a disease that causes abrupt involuntary jerky muscle movements. These jerks range from tiny twitches of a finger to movements so strong that the patient is flung to the floor, or objects held in the hand are hurled

across the room. Noise, light, or even attempts to sit up or hold a fork can trigger myoclonic movements.

There are many causes of myoclonus, but some cases are postulated to be due to a brain deficiency of serotonin. It is now generally agreed that certain patients with myoclonus respond to treatment with L-5HTP, sometimes being transformed from bed-ridden invalidism to the point where they can walk and take care of themselves.

There is, however, a problem—the drug costs about \$135 per month per patient. Having finally found a useful remedy, van Woert now has to fight for the funds needed to keep his patients from relapsing to their former state. Grants from the National Institutes of Health (NIH), several drug firms, and private donors have proved to be only stopgap measures. For the last two years, a National Myoclonus Foundation has helped raise additional funds.

The difficulty is that some of the common sources for drug-cost reimbursement are ruled out by a perverse twist of FDA regulation. Until a drug is approved for marketing, it is an "investigational drug" and patients cannot be reimbursed by Medicaid, Medicare, or private insurance companies. But no company is likely to sponsor L-5HTP for marketing because the number of patients needing it is so small. Requests for help in solving this dilemma have gone to Senators Kennedy, Magnuson, and Javits, and to Representatives Holtzman and Ottinger, all to no avail, while letters to Ralph Nader and his consumerist associate Dr. Sydney Wolfe have not been answered. And the several pharmaceutical companies that have expressed a willingness to market the drug are interested only if the development costs are likely to be modest.

There the matter sits. So far, various temporary expedients have sufficed to purchase just enough bulk from the manufacturer to allow private capsuling by van Woert. But it is a hell of a way to go about treating sick people.

Reasons for Orphanization

It is hard to know how many orphan drugs there are. The ones that have come to public scrutiny are probably only the tip of the iceberg. The Center for Disease Control in Atlanta,

for instance, has had to procure, stock, and distribute about forty biologic products for treating everything from botulism to snake bites and for preventing death from such varied diseases as encephalitis and tularemia; it also makes available eleven antiparasitic drugs. Most of these materials have never been licensed for marketing.

There are, as I have said, different reasons for the existence of drug orphans. One is the estimated size of the potential market. No matter how low the cost of development, it is difficult for a company to justify committing funds to a product that will never make any money or even cover its costs. And of course development costs are rarely low. Indeed these costs, which have risen dramatically in the wake of the 1962 Amendments to the Food, Drug, and Cosmetic Act, have become a major deterrent to the development of all drugs, but especially the orphans. In the pre-1962 days, drug companies could provide "prestige" or "public service" drugs without making an excessive corporate investment. Today, it takes them, on average, \$54 million and eight years of clinical work to bring a new drug to the U.S. market, even leaving aside the legal liability risks for the toxic effects that all drugs can produce. The problem for the public-spirited firm is that resources spent on "losers"—on the low-volume unprofitable drug—cannot be devoted to research on potential big "winners."

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Behind the excessive costs are the ever-increasing demands of the FDA's Bureau of Drugs. It is not too strong to say that the FDA never does anything that actually cuts the costs of drug development. Rather, each new regulatory fiat ups the ante.

Also, as noted, some orphan drugs are not patentable as drugs. The subsequent lack of exclusivity (or the fear of that lack) is a powerful deterrent to development, "use" patents being less attractive to firms than patents for chemical entities, and less enforceable.

But there is also a certain lack of imagination on industry's part. Dopamine testifies to that lack, and so, I suspect, will carnitine. Some disgruntled scientists have begun to refer cynically to the "NIH syndrome"—meaning not the National Institutes of Health, but "not invented here." If a company's scientists did not develop a particular idea or seek out a particular product on their own, it is not worth considering.

New Directions

Although few people are eager for the government to get directly into the business of producing and selling pharmaceutical drugs, we are beginning to hear demands for a degree of socialization of drug manufacture or for "orders" from government to "force" private industry to market orphan drugs. Senator Kennedy has on several occasions introduced legislation that would establish a National Center for Clinical Pharmacology, one of whose functions would be the study and development of orphan drugs. It is by no means clear from this proposal how this responsibility would be met.

Can anything be done to get around regulatory and industrial apathy while forestalling further governmental intervention in the drug industry? Back in the 1950s, the National Cancer Institute began to attack the problem of orphan drugs in its own area. Its initial approach was to contract with drug firms to stimulate badly needed cancer chemotherapy research, and the institute continues to work closely with industry at every level of development, from animal tests to clinical trials. Hundreds of thousands of synthetic and natural products have been screened. The results have been salutary, and patent problems with drugs discovered by such joint measures have been minimal. There is a similar program, at least in theory, at the National Institute of Neurological and Communicative Disorders and Stroke for the development of antiepilepsy drugs.

The FDA, for its part, could adopt less rigid rules for drugs of limited commercial value than for drugs of more general use. Whether it would need legislation to do so is largely moot. In the past this agency has been expansive in its interpretation of the law and

the legislative history whenever it has wanted to do something, and restrictive only when it has been reluctant to act. Be that as it may, the FDA is now suggesting, in proposals currently before Congress (S. 1045 and S. 1075), new approaches for orphan-type drugs that could in theory facilitate research and development. The effort enjoys the moral support of the agency's advisory committee on orphan drugs, whose recent report, though too general to give specific guidance, at least agrees that the problem deserves attention.

Special patent protection or market exclusivity for the private sector for a period of years would also be a help. So would tax incentives—particularly incentives to encourage innovation by small firms. It is paradoxical that the 1962 drug amendments, stimulated in part by Senator Estes Kefauver's antipathy to monopoly and concern for small business, brought about the high drug-development costs that have helped to destroy small pharmaceutical firms. Perhaps this trend could be reversed by passing legislation that allowed the formation of venture development firms enjoying favorable tax treatment. Small firms with limited staffs could, it has been argued, find it profitable to take a drug from the point of discovery through marketing approval, and then to license it to an existing drug firm that had distribution and marketing capabilities. Capital might be solicited the way oil exploration firms obtain funds for drilling costs. Such venture development firms could be associated with universities—following the model already being used successfully in Kansas, South Carolina, and Wisconsin.

IT IS DIFFICULT to be optimistic about orphan drugs, despite occasional happy endings to past stories. The problem calls for imagination and flexibility—qualities for which neither regulators nor regulated industries are notorious. Yet science has never been so poised for progress as at this moment. There will be breakthroughs. And when they come, they will quite probably be as different from today's drugs—our penicillins and prednisones—as today's drugs are from the calomel and cinchona of the last century. Rather like carnitine, perhaps. It would be a pity if they came into the world as orphans, never to be adopted. ■