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The Uncertain Future of Drug Design

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Why, you may ask, should the future of drug development be uncertain? Is there not a generally appreciated need for new drugs? Has not the fantastic pharmaceutical progress of the last four decades merely whetted our appetites for even greater medicinal advances?

The uncertainty does not derive from complacency about the deficiencies of our current drugs. The emergence of resistant bacterial strains emphasizes the continued need for development of new antibiotics. The magnificent contribution of levodopa to the care of parkinsonian patients nevertheless has not stemmed the inevitable downhill course of that disease. Chlorpromazine, useful as it has been in the treatment of certain schizophrenics, leads in some instances to irreversible neurologic damage and tardive dyskinesia. Severe rheumatoid arthritics find many of our current medicines inadequate or too toxic. Most solid tumors do not yield significantly to present therapy. A number of neuromuscular diseases are left almost untouched by any therapy. Therefore, it is clear that the future of drug development is not uncertain simply because there is no need for drug development.

Is the problem, then, that we have run out of ideas — the so-called knowledge depletion hypothesis? The answer to that must be a resounding *No!* If one reads any journal, or goes to any first-class meeting, one is overwhelmed by the exciting parade of new facts and potential leads. The enkephalins, the prostaglandins, the beta- and H_2-blockers, and similar developments provide hope for fantastic new accomplishments. We may, to be sure, have a problem in integrating such information into our gestalt or in being misled or confused by an embarrassment of riches (so-called "information overload"), but let us not be deceived into thinking that there are no new discoveries to be made.

Is the problem the absence of an apparatus for research and development? No, that certainly exists, within industry, in the universities, and in some government laboratories. So that is *not* the trouble

Well, then, what *is* the problem? The difficulties are multiple. The danger signals come from a series of disturbing developments, not all related to one another, but cumulative in their impact.

To begin with, there is a decline in the amount of effective dollars for national health research and development. We have seen a decline in real dollars allocated to research by the National Institutes of Health and the National Science Foundation, and a relative increase in contract research, which is the intellectual activity least likely to generate new ideas. The passions of Congress are unpredictable, and the federal roller-coaster pattern of alternating enthusiasm and apathy for specific projects results in wasteful allocations of funds, as we set up programs only to dismantle them a few years later.

Furthermore, there are a number of economic sumps draining off our resources. These include so-called "defensive" research by industry to protect old drugs, legal battles taking up time, energy, and lawyer fees, the cost of implementing "good manufacturing practice" regulations and "good laboratory practice" regulations, etc.

In addition, there are economic disincentives from the increasing cost of drug development. Our own estimates at the University of Rochester Center for the Study of Drug Development are that at the moment it is costing 55 million dollars and about 7 years of effort to bring a drug to market. These figures include (as they should) the expense that goes into doing research on chemicals that, in fact, never see the marketplace as well as the small number that do. There is an obvious intent on the part of drug regulators in the United States to allow generic manufacturers easier access to the market, which will in turn decrease patent protection, since at the moment, the burden of defending against commercial piracy falls on the originator. The FDA does not have any legal mandate to keep off the market unscrupulous companies who seek to circumvent valid existing U. S. patents. There has, furthermore, been a decrease in *effective* patent life down to about half of the 17 year period that is theoretically available, due primarily to the increasing length of time required to market a drug after the patent clock starts running.

The maximum allowable cost (MAC) program and the state-by-state repeal of antisubstitution drug laws are efforts that, regardless of their motivation, will inevitably lead to disincentives for innovative firms. On the international scene, we have seen more and more pressures on companies for cost containment in regard to reimbursement from national health schemes. All such moves represent short-term gains for the public, with little concern for their future impact. It is all terribly seductive because most people cannot see beyond the end of their noses, and there is simplistic instant gratification in the form of apparent (or even real) temporary savings on drug bills.

A third problem arises from increasing governmental interference in all aspects of drug development and drug usage. This is part of a large social pattern never envisioned by our founding fathers, who sought to limit drastically the powers of the federal government. Instead of this original intent, we see huge amounts of money and a large bureaucracy employed in the futile hope that productivity and creativity will be increased thereby. Instead, the public is finding itself not only less satisfied, but less free as well.

The latest evidence of this trend is the proposed Drug Regulation Reform Act of 1978. It starts out with a correct perception — i.e., that things are not well in Washington and Rockville, Maryland, in regard to drug regulation and development — but operates on a wrong premise, namely, that the troubles are due to bad law. In fact, our problems are not generated by bad laws but by bad implementation of the law by individuals in a regulatory agency motivated by a philosophy and an atmosphere that favors the obstruction of drug development. Many FDA employees operate in what has been described as a "siege mentality." They are under fierce pressures from all directions, and there is no reward for progress. Instead, the rewards are for not taking action, for holding back drugs. From time to time the system is changed by consumer pressures, as exemplified by the recent approval of the antiepileptic drug sodium valproate, but this is the rare exception that proves the rule.

The proposed solutions in this legislation embody fantastic new powers for a troubled agency that already has too much to do and too few good people to do it. We are told that the Secretary of HEW and the FDA Commissioner should be able to take drugs off the market more readily and that they will then allow drugs to be marketed sooner, but we are not told how the latter is to be accomplished. The knowledge that if it were up to the FDA Commissioner, saccharin would now be banned from the market does not make one comfortable about the possible abuses of the greater powers we are told they need.

The proposed law also raises the specter that drugs will not be allowed on the market unless they are shown to be better than drugs already on the market, or at least as good. Such a philosophy, if applied retrospectively, would eliminate

most of our antiepileptic and anticancer drugs. The regulators and legislators seem not to appreciate the fact that second, third, and fourth line drugs are needed as therapeutic backstops for patients who do not respond well to first line drugs that are on average, better or safer.

The law proposes that research on so-called "orphan drugs," i.e., those that are not likely to be developed because they are intended for small, unremunerative markets, should be the concern of a new clinical pharmacology institute. Anyone who knows anything about drug development realizes that another NIH institute (or, God forbid, an FDA institute!) set up to foster clinical pharmacologic research is not going to answer this problem.

The law also has built into it an increased number of "old" points in the IND-NDA process which will further increase the cost and time required to market a drug.

The law allows the FDA almost unlimited powers to demand studies on any aspect of therapeutic efficacy or toxicity, regardless of the indications for which the manufacturer plans to market the drug.

Good ideas, such as post-marketing surveillance and patient package inserts, may be forced upon us by this law before we, in fact, know how to achieve these goals safely and effectively. There is a Joint Commission on Prescription Drug Use which has been deliberating for some time now, with exactly the charge of making suggestions for post-marketing surveillance. Why can we not wait until the recommendations of this expert body come through?

We are told by the drafters of this legislation that the same standards should apply to all drugs. There are obvious advantages to bureaucrats in such inflexibility, but if this means that all old drugs or over-the-counter drugs will have to pass the test of modern, double-blind, randomized controlled trials, we will be in for a great deal more expense and trouble, or the elimination of many of these drugs from the market.

The hearings held in the Senate were carried out hastily and without invitations being tendered to some of the people one would have thought most knowledgeable about these problems, such as the last few FDA commissioners and FDA general counsels. Instead, one saw a parade of know-nothing consumerist advocates and lawyers. One would have to have a great deal more repect for the probity, wisdom, and imagination of people on the Washington scene than I have, to feel comfortable about this legislation.

What about the future? I believe it more likely that we will see increasing regulation, and increases in the time and money needed for drug development. I predict a decreased adventuresomeness in industrial research, and the elimination of small firms. There will be an increased tendency for research and development funds to move abroad and for human investigation in drugs to be done there first, as well as a decreased interest on the part of academic investigators in drug research.

Is there any hope? Not a great deal, but I would submit we have to keep trying to improve the situation. One hope lies in educating the public and politicians, through efforts by academic experts and by the increased participation in public discussions of the true consumers, i.e., the sick, their relatives, and people representing disease-oriented foundations. The Bible tells us that "where no counsel is, the people fall; but in the multitude of counselors there is safety."

Majority rule is really the rule of minorities either banded together or working all too effectively on their own. We must avoid the tyranny of minorities. It is pathetic to see how much mischief can be achieved by certain lawyers, physicians, and journalists, who believe that they are the only ones with a pipeline to eternal truth. In fact, these people often represent no one but themselves.

It is a pity that most scientists have no stomach for battling in the me or in the halls of Congress because that is where most of the battles are, in opinion, going to be either won or lost.

Perhaps the best thing that we could do would be to have Commissio Kennedy, whose half-life in office will probably be as short as his predecesso replaced by someone like Alfred Kahn, the present chairman of the Civil Ae nautics Board. On May 24th, the Rochester, New York, *Democrat and Chro cle* carried the following quotation by Kahn: "Before I am through I am go to get this industry so competitively structured that you will never get it b together again — I don't mean the industry; I mean the Civil Aeronau Board." He went on to say that regulatory reform for the nation's airli "means returning the industry to private enterprise. It means entrusting pi tection of the public to competition." He said that this does not mean rela government concern for airline safety: "If anything, we have to increase vigilance of direct regulation of airline safety."

To return to the Bible. One proverb says, "Where there is no vision, people perish." But another reminds us: "Whosoever diggeth a pit shall therein."

Let us hope that the good Lord allows the enemies of drug developn to fall into the pit, but I would ask one favor of the Lord, in this regard. know that "a thousand years in thy sight are but as yesterday" but could just hurry it up a bit, Lord? Some of us think that things have been goi hell much too long.

President Buerki (left) presents the 1978 Rho Chi Lecture Award to Lo Lasagna, M. D. at the 54th Annual Convention held May 14, 1978 in Mo Canada.