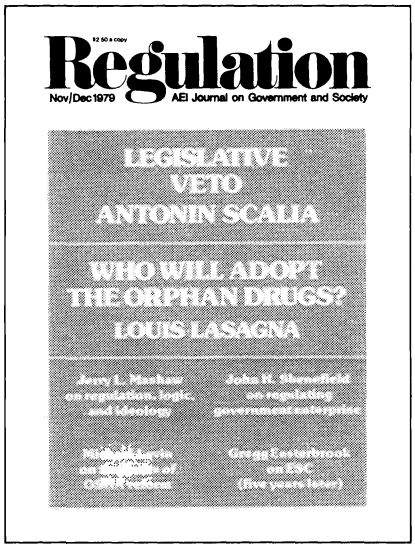
Letters

We welcome letters from readers, particularly commentaries that reflect upon or take issue with material we have published. The writer's name, affiliation, address, and telephone number should be included. Because of space limitations, letters are subject to abridgment.



Adopting Orphan Drugs

TO THE EDITOR:

Louis Lasagna's article, "Who Will Adopt the Orphan Drugs?" (November/December), correctly points out that the FDA's demands for costly long-term preclinical and clinical studies have served to deter research, development, and manufacture of "public service" or orphan drugs by pharmaceutical companies. As he concludes, the FDA's regulatory processes and the pharmaceutical companies' goals are not compatible with the development of orphan drugs.

Along with Dr. Lasagna, I am not optimistic that the problem of orphan drugs will be solved. My attempts to interest pharmaceutical companies, government agencies, and the private sector in assisting in the development of L-5-hydroxytryptophan for myoclonus have been futile because of the uncompromising positions and self-interests of the parties involved. By definition, orphan drugs are unprofitable and hence unattractive to pharmaceutical companies whose interest in development and manufacture of new drugs is proportional to their anticipated financial returns. After all, the companies' major obligation is to stockholders, not patients. As the costs of FDA regulations increase, the number of orphan drugs and orphan diseases will increase, which portends even greater problems for the future.

The FDA's position is that its duty is to *regulate* drugs for safety and efficacy, not to facilitate research, development, and distribution of either profitable drugs or those with little commercial interest. As for the National Institutes of Health, the high costs of drug development have kept it from getting involved with this problem, except for the heavily funded National Cancer Institute and the epilepsy branch of the National Institute of Neurological and Communicative Diseases and Stroke. Moreover, little help can be expected from consumer organizations such as Dr. Sidney Wolfe's Health Research Group. These organizations are predominantly concerned about the safety of new drugs and favor premarketing tests and safeguards even more stringent than those which orphan drugs cannot presently meet. Finally, a succession of committees, task forces, and legislative proposals have produced at best only hints of possible solutions and vaguely defined incentives.

If we agree that the present system limits drug development to only profitable diseases and ignores scientific leads for orphan diseases, and if we concur that this is unfair and contrary to the public interest, then stronger, more concrete measures are needed. These could include mandatory government contracts, increased NIH support for drug development, or making orphan drug development one requirement for the licensing of ethical pharmaceutical companies.

Perhaps the most encouraging recent development is the concerted lobbying effort on the part of the members of voluntary health organizations such as the Committee to Combat Huntington's Disease, the Epilepsy Foundation of America, the Tourette Syndrome Association, the National Myoclonus Foundation, and others. Congresswoman Elizabeth Holtzman (Democrat, New York) is one legislator who has responded to their appeal and who is formulating legislation which should offer more direct and precise solutions to this problem.

Melvin H. Van Woert, M.D.,
Mount Sinai School of Medicine

TO THE EDITOR:

Dr. Louis Lasagna's article certainly points up the despair of those today who must face death prematurely, for want of effective treatment.

We seem to have forgotten the morality of cure—for we dwell instead on care. Care is certainly kind. Cure, however, is kinder. Ultimately, all patients want nothing more than to be rid of their disease. They care little for insurance that permits them to suffer the disfiguration of arthritis or the painful agony of oncoming death from cancer.

The ridding of disease can come only through innovation—the genius which discovers the cure. What are the ingredients of innovation in medicine? They are ideas and the testing of these ideas in medicine, through clinical research. Block the transition of the ideas to their clinical testing and innovation suffers. This is precisely what is happening today and threatens to continue to happen. Barriers ranging from regulatory to legal to moral have virtually blocked the entrepreneur in the pharmaceutical world from clinically testing his ideas.

With natural substances the problem is even more critical. Because of the nature of our patent laws, strong patents are easier to obtain for artificial molecules synthesized by chemists than for natural substances. The economics, therefore, of spending millions of dollars to develop safe natural substances is not nearly so promising as that of very strange molecules. Thus, in an irresponsible way, the Congress continues to encourage production of artificial molecules that assail the organ systems of our bodies and

cause a myriad of adverse effects ranging from generalized weakness to cancer.

The human body has a wonderful track record of combatting disease from the time of conception to our final hour. Does it not make sense to harness those substances that continually and successfully fight off the daily enemy, the invaders of the body and the mind? The greatest breakthroughs in medicine—steroids, digitalis, antibiotics, vaccines, and so on—all involve natural substances, not some new molecule conceived by chemists.

As Dr. Lasagna pointed out, it was thirteen long years from the time when I first postulated that carnitine would have a beneficial effect in heart disease (idea) to the testing of the hypothesis clinically (clinical research). After the thrill of the clinical confirmation of the idea came the depression of the economics of medicine. Carnitine is a natural substance with much promise but weak patents. This unfavorable combination is not sufficient to arouse the interest of the U.S. pharmaceutical industry.

The Congress, spearheaded by Senator Kennedy, increasingly blocks innovation in medicine by preaching the politics of care. Congress, therefore, is without doubt the greatest enemy of the patient. Perhaps a wiser presidential candidate will dare to raise the issue of "cure" instead of "care" to the public. What better way than to begin with nature?

Stephen L. DeFelice, M.D.,
President, Biocarn Ltd.

TO THE EDITOR:

Louis Lasagna's article is a clear exposition of a critical unsolved problem. He suggests a number of solutions: (1) increased activity by the federal government, (2) less stringent regulations for the release of orphan drugs, and (3) patent protection, as well as market exclusivity for venture drug-development firms.

Rather than expand government support of drug development, I would prefer the approach of greater participation by the pharmaceutical industry. My suggestion is that a group of the major pharmaceutical companies, or perhaps the Pharmaceutical Manufacturers Association, appoint a panel of distinguished scientists outside of the industry to study the problem and to invite scientists working with potentially useful orphan drugs to so advise the panel. The panel could then review each case to determine whether available channels had been exhausted, and if not, to guide the investigator to a company with possible interest in the drug. If no takers were found, the panel would then review the merits of the investigators' proposals for their respective drugs and compile a list ranked according to merit. The companies represented in the consortium then would decide, possibly on a rotational basis, how many orphan drugs they could assist in developing.

This plan has several advantages. First, an estimate of the numbers of orphan drugs requiring and deserving development would be obtained. Second, an enthusiastic investigator would have the opportunity of presenting his or her drug to a peer review panel outside the industry, thus reducing criticism of the industry when drugs are refused, as many must be, on the basis of merit. Third, if the number of meritorious orphan drugs were found to be large, then a better case could be made for pressing for the long-range solutions suggested by Dr. Lasagna. Fourth, like dopamine, some of these drugs ultimately may prove to be profitable. The companies involved in the consortium could consider plowing back profits into future development.

There will undoubtedly be many objections to this proposal. I would be interested in knowing them.

Finally, Dr. Lasagna and I agree that there is a certain lack of imagination on the part of industry. I must, however, partially disagree with his statement depicting the psychology of the house scientist: "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." In my opinion, orphan drugs discovered in industry are rejected also and for the same reason as drugs outside of industry—cost. At best, it is extremely difficult to estimate the market of a totally innovative product and, in view of the extraordinarily high cost of development, the refusal by the pharmaceutical industry to proceed with some of these drugs is certainly understandable. This brings us to perhaps the most important argument of Dr. Lasagna's paper: a long-term solution will require a more rational and economical path for development of new drugs.

Leon I. Goldberg, M.D., Ph.D.,
The University of Chicago

TO THE EDITOR:

Dr. Lasagna, in his usual lucid and incisive style, calls attention to a major deficiency in drug development in our country. He correctly points to the development of new anticancer drugs as an area where the government played a major role. That program, begun in approximately 1956, has proven enormously successful: at least thirty clinically useful anticancer drugs are commercially successful and are now available to physicians.

There remain, however, major areas of drug development where commercial potential is limited and the needs of individual patients and their physicians are great. These are the so-called orphan drugs. For example, in our own clinic we have found that etiocholanolone is highly effective at mobilizing granulocytes into normal donors' peripheral blood, increasing the efficiency of granulocyte collection by approximately 100 percent. This drug is no longer available to us or to the donors and we have to expend enormous amounts of time and energy using other drugs that are less effective.

Scientists, physicians, and patients alike have come to the view that FDA regulations are now clearly oppressive. As Dr. Lasagna points out, the enormously increased cost of complying with FDA requirements has swelled the number of drugs that fall into the orphan category. It seems to me that the federal government now has an opportunity to undo some of the harm it has inadvertently done to people who desperately need these drugs. The agency could do this by providing direct support to the pharmaceutical industry for the manufacture and distribution of precisely these orphan drugs. As with the cancer drug-development program, when the potential usefulness of an agent is clearly demonstrated, the federal government could support its preparation and manufacture until the scientific community determines the agent to be (1) of proven value and potentially financially successful, whereupon the drug industry could assume responsibility for it; or (2) ineffective, unnecessary, or superseded by another drug, in which case it could be discontinued.

It is time, I believe, for the public to call upon its government to implement such a program. In my personal view, the FDA should be given the responsibility and opportunity to break with its negativism

and to contribute and stimulate the development of needed orphan drugs.

Emil J. Freireich, M.D.,
M. D. Anderson Hospital
and Tumor Institute

TO THE EDITOR:

Dr. Lasagna is correct that there *are* orphan drugs, as was clear from my previous vantage point as a drug regulator. More important, there are orphan patients suffering from illnesses rare enough so that there is little commercial interest in finding a drug to cure them.

Epileptics are among those patients, and there is indeed a program for developing antiepileptic drugs at the National Institute of Neurological and Communicative Disorders and Stroke. But it is not only a program in theory, as the article suggests, but a practical and remarkably effective one, that has played a key role in getting three new antiepileptic drug applications approved in the United States since 1974, after a hiatus of fourteen years without even one new primary antiepileptic being introduced in this country. Intriguingly, this program is only one of eight or more such government programs, proceeding quietly with varying success—ranging from the NASA-like cancer drug program to a program aimed at new iron chelators for Cooley's anemia patients.

Dr. Lasagna made two arguments deserving of qualification. One relates to the difficulties in developing new drugs. His anecdotes of orphan drugs could be multiplied many times, since for each marketed drug there may be 3,000 compounds that were orphaned, or even stillborn, in the development process. That's the nature of drug development and nobody says it's easy. Of the drugs dropped along the road, some have had more vociferous supporters than others. The examples he selected may be major improvements, or they may turn out to be just clever ideas that did not work. For example, the facts are not all in on 5-HTP, even though it has seemed to help a few patients a great deal.

To move on to the second argument, I do not believe the picture will be as black as Dr. Lasagna does once the facts *are* in. In the past, a number of orphan drugs have found a home once a quantum of evidence was reached. Dr. Lasagna and the FDA differ on what the quantum is, but the FDA is not alone in believing toxicity testing and controlled trials are valuable before distributing a compound nationally. Although the FDA has at times been unnecessarily rigid, it has played a major role in facilitating marketing of orphans like L-dopa and nitroprusside. As for 5-HTP, Dr. Van Woert is continuing his studies (with government support). That is not to say there aren't many problems left to solve, but I do not believe we need to share all of Dr. Lasagna's pessimism.

Barrett Scoville, M.D.,
National Institutes of Health

LOUIS LASAGNA responds:

Dr. Goldberg's comments, like those of the other correspondents, are well taken. But the "not invented here" syndrome is not my own assessment of the state of affairs, but what "some disgruntled scientists have begun to refer to cynically" as a cause for orphanization.

Reforming OSHA

TO THE EDITOR:

Michael Levin's "Politics and Polarity—The Limits of OSHA Reform" (your November/December issue) is a refreshingly frank and insightful analysis of the problems many of us in Congress have faced as we have tried to improve OSHA. As Mr. Levin points out, there is a clear need for an effective federal program to improve worker safety and health, and OSHA has not met that need adequately. Indeed, the agency has become probably the most despised federal agency in existence. Moreover, plans to seek reform have been derailed by the bitter (or, in Mr. Levin's words, "almost petrified") polarization of management and labor—and I might add, of many members of Congress.

Your readers may be interested in a concrete reform effort now under way in the Senate. On December 19, I introduced the Occupational Safety and Health Improvements Act of 1980 (S.2153, cosponsored by a broad bipartisan coalition that includes Senators Harrison A. Williams, Jr. (the principal author of the original OSHA bill in 1970), Frank Church, Alan Cranston, and Orrin Hatch. This bill would concentrate OSHA's safety enforcement activities on workplaces having poor injury records and would create incentives for industry itself to reduce occupational injuries and illnesses. In short, the legislation seeks to shift OSHA's role from that of a policeman to something more like that of a cooperative partner in improving workplace safety and health. Under the bill, workplaces with good safety records would be exempt from most safety inspections and, in addition, those that maintained an active safety program (including outside consultation and a safety committee) would also be exempt from most civil penalties for safety violations.

These proposals are similar to suggestions made in Mr. Levin's article and in the report of President Carter's Interagency Task Force on Workplace Safety and Health, of which Mr. Levin was deputy director. Now, for the first time since OSHA was created, we have significant movement toward depolarizing OSHA and building a consensus for meaningful reform.

Richard S. Schweiker,
United States Senate

Government Enterprises

TO THE EDITOR:

John Shenefield deserves credit for calling attention to the federal government's growing propensity to blunder into direct control of formerly private enterprise. But he should pick his quarrel with the blunders. Instead, he presents an argument against government enterprise in general. His case rests on three points. Of these only the last is valid, and when taken alone it points to a different conclusion.

Shenefield's first point is that government enterprises skew pricing signals in undesirable ways, whereas in the competitive private sector "the traditional assumption has been that . . . price will tend to be aligned with marginal cost." In fact, marginal cost pricing neither is nor can be an authentic policy objective. Shenefield concedes that stringent conditions must be met before marginal cost pricing will actually prevail. He ignores the further conditions that must apply for it to be desirable that marginal cost pricing prevail. These are set out in J. de V. Graaff's classic *Theoretical Welfare Economics*, Chapter 10: "The conditions which have to be met before it is correct (from a welfare standpoint) to set price equal to marginal cost in a particular industry are so restrictive that they are unlikely

(Continues on page 59)

(Continued from page 4)
to be met in practice. The survival of the marginal cost-pricing principle is probably no more than an indication of the extent to which the majority of professional economists are ignorant of the assumptions required for its validity. How else can one account for the glib advocacy of the principle in a society where the marginal rate of income tax is certainly not zero, where optimum taxes are certainly not imposed on both imports and exports, where external effects in consumption are of the first importance, where uncertainty and expectation play a major role in making life worth living, where . . . ?"

The rule of "price according to marginal cost" simply has no desirable properties in the real world. Hence Shenefield's case against introducing redistributive objectives into product pricing fails, and so his general argument in favor of private over public decisionmaking is unfounded.

Shenefield's second point is that government enterprise entails "the loss of discipline inherent in private competitive markets." Loss of discipline by comparison with what? Were Chrysler and Lockheed paragons of competitive discipline before the federal government intervened to guarantee their operations? Hardly. Is the tariff protection the federal government accords to domestic producers of steel, shoes, textiles, Florida tomatoes, and Idaho sugar beets the cause, instead of the consequence, of competitive failure? Hardly. Have General Motors and Ford been inspired to be less competitive than they would otherwise be by the recent transformation of Chrysler into a public charity case? It strains credulity to think so. Or perhaps Shenefield is again making an implicit comparison between simple theory and complex reality—an implicit comparison between the hypothetical private competitive firm of the textbook and actual public and publicly protected private enterprise. If so, his is a case for a cloud-cuckoo-land that never was and never will be.

Shenefield's final point is that public enterprise too frequently escapes the public accountability that government now imposes, through regulation, on the private firm. On this he is right. TVA had a dismal environmental record, the Postal Service lags on occupational safety, congressional employers are exempt from equal opportunity laws —the list could go on. But if this is the problem, then the solution is to extend the substance of government regulation to public business.

More broadly, Shenefield's case against extending the public's jurisdiction is misplaced. The issue should not be whether the federal government should respond to pleas from failing enterprise for assistance, but how. There is a good case for preventive medicine—for economic planning to help keep the private sector productive and solvent. There is an excellent case for the development of a systematic policy to deal with the threat of large-scale industrial failures, instead of the ad hoc crisis management of policy today. But, whether it is well or poorly done, the public sector's responsibilities will continue to grow. There is no return to laissez faire.

James K. Galbraith,
University of Maryland

JOHN H. SHENEFIELD responds:

Professor James K. Galbraith's agreement with my point about the nonresponsiveness of public enterprises gives away his game. I would paraphrase his lengthy quotation from J. de V. Graaff in this way: "The conditions which have to be met before it is correct [from a welfare standpoint] to submit the resource allocation decisions for a particular industry to the political process are so restrictive that they are unlikely to be met in practice. The survival of the principle that basic decisions on price and output ought to be made through a nonmarket mechanism is no more than an indication of the extent to which some economists are ignorant of the assumptions required for its validity. How else can one account for the glib advocacy of the principle in a society where the dynamics of electoral politics may compel public officials to disregard their own vision of the 'public good' in response to pressures from mass-membership organizations, campaign fund donors, and single-issue spokesmen; where significant decisions are made not by elected officials, but by the bureaucracies of both Congress and the executive branch and by independent agencies; where key decisions are subject to review by judges with lifetime tenure; where much of the media's attention is focused on image and conflict, rather than substance and resolution; where high turnover in the ranks of public decision makers gives rise to a tendency to leave difficult problems to one's successors; where . . . ?"

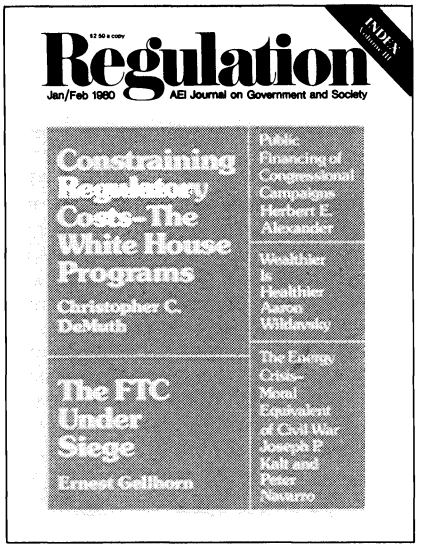
Thus, one can only say that the rule of "price according to political decision" simply has no desirable properties in the real world—or only does if one's analysis of public sector decision making is itself divorced from reality. Indeed, one has only to look at a centrally planned economy slightly to our south or at the economic productivity of countries that have come under the rule of philosopher-kings (or ayatollahs) to feel more than a little justified in believing that nonmarket pricing has more than its fair share of trouble.

What then? I submit that imperfect as the system of cost and pricing signals may be, the monetary cost of producing the next unit of a commodity and the price that potential customers are willing to pay for it tell us more about the value of that next unit of output than any other system of resource allocation of which I am aware. It is closer to the true measure of societal benefit than the beliefs of a congressional appropriations subcommittee staff director or an executive branch budget officer on what is the appropriate funding level for a public enterprise, and certainly a lot closer than some bureaucrat's perception of what is good for us all.

Finally, Galbraith's rejection of marginal-cost pricing has one important implication: the elimination of competition among providers of goods and services, be those suppliers public enterprises or private ones. For a rejection of marginal-cost pricing implies the existence of cross-subsidies: if price and cost have no relationship, then the production of some commodities will simply be more profitable than the production of others. Competitors, if permitted to exist, will attempt to sell that lower-cost product at a lower price and thus deny the enterprise the revenue needed to cover costs incurred elsewhere. The implication is that steps may be taken to prevent competition, so that the cross-subsidized apple cart is not overturned. One need only recall the "cream-skimmer" cries raised by protected firms in the battle to open entry into the airline, trucking, and communications common-carrier industries to realize the vested interests generated by systems that create, or allegedly create, cross-subsidies. Fortunately, these arguments are now being rejected by Congress and regulatory agencies. In a word, those same public institutions in which Galbraith

would place his faith have moved, correctly and decisively, in favor of competitive, cost-based pricing mechanisms.

If "there is no return to laissez faire," it is because that blissful state never existed. Instead, what we are now witnessing is a return to a healthy respect for the market system as an allocator of resources and the realization that public intervention, as a general rule, is not a panacea for all problems.



Campaign Finance

TO THE EDITOR:

Herbert E. Alexander's "Public Financing of Congressional Campaigns" (*Regulation*, January/February), makes an ingenious proposal. Insofar as campaign finance lies at the root of our representation problems, his solution may be the best available. Insofar as improved financing of campaigns affects other aspects of representation—political parties, for example—the benefits of Alexander's plan may be more extensive. But, are problems with congressional campaign financing more than annoying symptoms of major failures elsewhere in our system of representation?

Among the basic failures in representation, to which campaign financing is related chiefly as a symptom, are the following: (1) Congressional districts are now more populous and more diverse economically than were most states when our system was established. (2) Along with that, and partly because of long sessions, members of Congress are remote in both geography and social space from their constituents. (3) Nationally organized special interests are able to communicate their desires to members of Congress more directly, more expeditiously, and more continuously than can less organized constituencies. (4) Communication between Congress and its constituents is primarily via the mass media, which are not responsible in either the legal or the political sense.

Does anyone believe that the best possible method of financing congressional campaigns will alter, substantially, even one of the above? Without altering them all, is it possible to restore our system of representation to a condition of vigor and public esteem?

Ivan W. Parkins,
Central Michigan University

TO THE EDITOR:

. . . Herbert Alexander's idea of floor grants rather than matching funds for candidates is not new. It has been around from the very beginning of discussions on public campaign financing and has been repeatedly rejected as thoroughly impractical. Of the 435 House seats up every two years, only about 100 are ever really in contest. The idea of providing $30,000 or $40,000 of taxpayers' money to each of the other 335 certain winners and 335 certain losers is ludicrous.

His scheme of providing candi date funding through the political parties can only strengthen those parties and make members of Congress more responsive to party direction if the party has authority to arbitrarily give or withhold the funds. But Congress is certainly not going to vote this authority to any party officials, nor should it.

Dr. Alexander is an authority on campaign financing. The works of his institute, the Citizens' Research Foundation, have contributed much to the general understanding of the subject. We all owe him a debt of gratitude. Having said that, I hasten to add that this, his most recent suggestion, defies logic, experience, and the will of the people. He proves Lord Acton's view: "There is no error so monstrous that it fails to find defenders among the ablest of men."

For 200 years we had a system of financing campaigns in the United States that worked, not perfectly but certainly adequately. Then, the reform wave of the 1960s and 1970s brought the idea that the political influence of the richest and strongest and the poorest and weakest could be equalized through public financing of elections and by limiting contributions and expenditures. Make no mistake, this was and continues to be the objective.

Have the reform laws of 1971 and 1974 with their restrictions and partial public financing of presidential campaigns achieved their goals? Certainly not. Nature and the system simply exchanged the big contributor for the big collector; the Supreme Court found half the law to be constitutionally invalid; and political action committees became the vehicles of the hated "special interests."

If anyone really believes that a majority of the public wants taxpayer financing of campaigns, he needs only look to the tax returns for rebuttal. Each year 85 million taxpayers vote on the subject and reject the proposition three to one.

It seems to me that Dr. Alexander and other advocates of campaign reform should stop tinkering with machinery that is not broken. They should admit that the adjustments made in 1971 and 1974 have not improved public confidence in either the process or elected officials. They should urge repeal of the 1974 law entirely and the public financing provisions of the 1971 law.

Congress should stop listening to Common Cause's cry that senators and representatives are bought through campaign contributions. If we can believe what we have read about "Abscam," the only official who turned down the preferred cash was the one who was offered a campaign contribution.

Thomas F. McCoy,
Washington, D.C.

HERBERT ALEXANDER responds:

Congressional public financing is not a panacea, and I did not seek to give that impression in my article. Public funding may not materially affect directly the four points made in Professor Parkins's letter, but it is a logical—and needed—next step in the search for an improved electoral system. Tom McCoy makes a number of points worthy of debate, which I have been carrying on with him for a number of years. I would only suggest that public funding is designed to, and perhaps would help to, increase the number of marginal house seats. McCoy is correct in stating that our present system is not sufficiently competitive, but adoption of public funding would at least have a chance of making it more so. ■