Drugs and the Brain and Society

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When first asked to prepare a series of lectures on human values, I felt strangely disquieted. I am a physician, a psychiatrist, and a research scientist concerned with how drugs affect the brain. My colleagues do not often speak professionally about *values,* which are not generally regarded as appropriate for scientific inquiry. And yet, on further reflection, I have little doubt that I and all of my scientific colleagues are enmeshed each day in our scientific research in the pursuit of human values. For every practicing scientist the most important activity is the choice of a scientific question. We don't often acknowledge this at a conscious level, but our choices of scientific direction are dictated as much by human values as by purely "scientific" considerations.

GULFS: ACADEME, INDUSTRY, AND SOCIETY

As science becomes more and more important in determining human destiny, it becomes progressively more difficult to regard scientific inquiry as a pure form of intellectual operation. The role that science plays in our society and how scientists go about their business is influenced profoundly by economic considerations. As the crunch of Western economies worsens in the last decades of the twentieth century, decisions on how to allocate monies for scientific endeavors become ever more stringent. I suspect that the politicians who constitute our national leaders do not adequately appreciate the real stringency of these considerations. They speak of the seeming decadence of Western societies and the need to revitalize them. They talk about programs to enhance "real" productivity. It is only through basic scientific and technological advances that our modern prosperous Western society has been possible. And it is only through further technological innovation that we shall overcome the debilitating effects of energy scarcity and social upheaval.

Here scientists and politicians come into conflict. Scientists value more than anything else their freedom of inquiry. The best scientists will not tolerate even the faintest hint of direction from administrators identifying for them what should be the "bottom line" of their research. The scientists are right in the sense that one cannot legislate scientific discoveries. According to this model, the best way to attain applied ends is not to seek them directly. Instead, the government and industry should subsidize fundamental *undirected* research in large amounts, with scientists following their whims wherever they might lead. Sooner or later they will stumble upon something of benefit to mankind.

The skeptical politician has some justification in questioning this approach. It sounds too much like the scientist is requesting a blank check for his "fun and games." What is the evidence that this leisurely meandering will in fact solve large and urgent problems confronting society? Thomas Edison may have tinkered in his laboratory, but he in fact directed all his efforts toward specific, concrete, and socially useful goals. He deliberately set out to develop an electric light bulb and a phonograph record. No "fuzzy" thinking percolated in Edison's mind about the "fundamental basis" of light or sound.

Why should the government be supporting basic research at all? Since research such as that of Thomas Edison paid off so handsomely in monetary terms, it is the proper function of industry. Indeed, most industrial concerns spend between two and ten percent of their assets annually in what is designated "basic research." The advocate of basic science usually responds to this reasoning by pointing out that a purely applied approach to science is not likely to result in genuine breakthroughs. The most frequently used analogy relates to polio. The philosophy of applied science would be to develop more efficient iron lungs. Basic research on tissue culture which permitted growth of the polio virus and development of the polio vaccine was fundamental science not directly related to any given disease. On the other hand, it could

be argued that growing viruses in tissue culture is, in fact, a very straightforward tool relevant to vaccine development, which any sensible drug company would undertake with simple profit motives in mind. Moreover, it could be argued that basic scientists' undue reluctance to think about the practical ramifications of their research has in fact retarded practical applications and may have even delayed the development of the polio vaccine. In other words, far more basic scientists were playing around with tissue culture as a scientific curiosity than were focusing upon how to exploit it for therapeutic purposes.

The extent of the conflict between the desires of basic scientists and the goals of industry and society as a whole varies with the field of science. Historically, the conflict has been somewhat less in physics and chemistry than in biomedical research. The payoff of basic physics research in terms of atomic and hydrogen bombs, transistors, television, and computers is well known. Because the practical applications of physics research are sometimes so awesome even to the most satedly sophisticated researcher, physicists in general do consider industrial applications and welcome employment by industrial concerns rather than universities. The same is true of organic chemistry, especially synthetic organic chemistry. The slogan of the Dupont Company, "better living through chemistry," is dramatically exemplified in so many instances that many chemists are inspired to participate in the commercial chemical endeavor as much out of fascination as financial incentive.

Biomedical research seems to be one area in which a gulf still exists between basic research and practical application. I see this often in my own work. Drug companies employ large numbers of chemists and pharmacologists. The level of technical and theoretical expertise of the synthetic organic chemists in the drug industry is generally as high and sometimes higher than the level obtained in universities. This is often not the case with pharmacologists and biochemists. The best of these researchers remain

on university faculties or in research institutes. They frequently regard their colleagues at drug companies with disdain. The breach is intellectual as well as social. Biochemists and pharmacologists in universities tend to be unfamiliar with the major therapeutic problems of medicine being attacked by the drug industry. Similarly, the pharmacologists in the drug houses are often unaware of the latest advances in molecular approaches to the bodily substrates of drug action.

What are the reasons for this gulf between basic and applied science in biomedical research? Why is this less apparent in chemistry and physics? I suspect the answer relates in part to the level of sophistication of the various scientific disciplines. Physics and chemistry have advanced as sciences to such a point that one can translate basic findings quite effectively into practical applications. Such developments have taken place much more slowly in biomedical disciplines, simply because the science of medicine itself is less advanced than chemistry or physics.

Why do I focus upon these discrepancies in the "scientific" status of physics-chemistry versus medicine? Most people knowledgeable about these areas would surely agree and indeed accept the discrepancy as almost a truism. Medicine developed from a concatenation of physics, chemistry, biochemistry, physiology, and anatomy. Surely, putting all of these fields together to study bodily function in disease and its treatment is a more complex enterprise. I have chosen to focus on this area because I feel we are positioned historically for a major change. Much of biomedical research seems to be reaching a critical threshold over which basic findings may flow rapidly and readily into therapeutic applications. I fear that the scientific community does not adequately appreciate this changing status of biomedical research. Moreover, even those who are aware of the rapid developments in biomedical science don't appreciate how these developments must alter the mental set of biomedical researchers. The researchers themselves may not be primed to shift old habits of thinking. Instead of

pursuing a scientific problem in isolation, perhaps they should be searching more and more for therapeutic spinoffs.

Scientists are not the only ones who should be aware of these changes. Government funding agencies may wish to reorganize some of their approaches to biomedical research support. For instance, bureaucratic separations of clinical and preclinical research might tend to preclude links between basic and applied findings. Medical schools may wish to bear these issues in mind in planning departmental organization, which presently separates clinical and preclinical entities. Industrial concerns may wish to foster greater interaction between company biomedical scientists and university researchers. Developing a cadre of outstanding fundamental scientists, such as molecular biologists, within industry may not be easily accomplished, at least in the near term. It may be desirable for industry to support such research in the university providing relatively unrestricted funds with only an understanding that company officials may visit the university freely and have "first refusal" in commercial development of new discoveries.

THE DISCOVERY OF MODERN PSYCHOTROPIC DRUGS — ANTISCHIZOPHRENIC NEUROLEPTICS AS A PARADIGM

The notion that basic and applied medical sciences should begin speaking more closely to each other does not in any way preclude a strong emphasis on fundamental research in all the physical and natural sciences. One of the most profound lessons learned by practicing researchers is that we can never predict where lies the truth. Though the National Institutes of Health in the United States are organized into individual institutes with specific disease designations, all practicing biomedical scientists know well that the crucial breakthrough in a field such as cancer may emerge from an unrelated area, be it allergy studies, transistors, or meteorites. Moreover, while therapeutic ramifications of basic discoveries must always be borne in mind, it can be a

tragic error to over-organize and over-target research toward specific goals. A good scientist toys with the ramifications of his research alertly, but playfully, ready to shift direction in midstream. Plunging straight ahead in a doggedly determined and almost blind fashion too often results in squandered funds and disillusionment.

In brief, many of the advances in medicine over the past century have been serendipitous, especially in drug development. A case could be made that basic research has not played an overriding role in developing major medical therapies. However, things are changing rapidly. To ensure the optimal enhancement of medical research and new therapeutic applications, it is crucial that systematic efforts be made to integrate preclinical and clinical enterprises in both university and industry. There is a sense of urgency about all of this, because the rapid pace of scientific advance in medicine suggests that rewards in alleviation of human misery are considerable. The seemingly unmeetable challenges of viral illnesses, cancer, heart disease, and mental illness may yield to modern approaches. Even a single major breakthrough in any of these areas could influence the quality of human life in a profound way.

Let me illustrate some of these points from my own small world of psychopharmacology.

The most important drugs in psychiatry all made their appearance between the mid-1950's and early 1960's. The antischizophrenic drugs, generically called neuroleptics, were introduced into psychiatry in 1952, when chlorpromazine, the phenothiazine neuroleptic, was first employed in treating psychiatric patients in Paris. The antidepressant drugs, comprising the monoamine oxidase inhibitors and the tricyclic antidepressants, appeared in 1957. The first drug recommended as an antianxiety agent, meprobamate (Miltown, Equanil) was marketed in 1955 and prompted a search for other antianxiety agents which culminated in the appearance in 1960 of chlordiazepoxide (Librium) and, two years later, of diazepam (Valium).

This spurt of novel psychotropic drugs in less than a decade is all the more remarkable considering that, essentially, no major psychotherapeutic drug had appeared before 1952. Moreover, since Valium was first marketed, few truly innovative psychotherapeutic drugs have been introduced. There is a general sentiment that the paucity of novel psychotherapeutic agents in the two decades from 1960 to 1980 has resulted at least in part from overly stringent practices of drug regulatory commissions in various companies, especially the Food and Drug Administration of the United States. However, this issue is not the direct concern of the present essay. Rather, let us review the development of a few psychoactive drugs to ascertain what factors facilitated or hindered their emergence.

Dyes. The history of the development of chlorpromazine has been elegantly reviewed by Swazey.[1] She makes a strong case, which enjoys agreement from many researchers in psychopharmacology, that a multitude of factors were involved, most of them unrelated to therapeutic concerns for schizophrenia. The first such factor seems to be the emergence of the dye industry. Synthetic organic chemistry and the development of a large dye industry, which spawned the major drug companies, can be traced to a specific point in time. In 1856 William Perkins prepared the first synthetic dye, aniline purple or mauve. Up to that time natural dyes had been the only ones available and were quite expensive. By contrast, mauve was readily synthesized and much cheaper. It soon became apparent that synthetic dyes could revolutionize the textile industry, so many chemists became involved in their development.

The mid-nineteenth century was a dynamic period in the development of synthetic organic chemistry as a meaningful scientific discipline. The growth of the dye industry was dependent in large measure on experimental and conceptual advances in

[1] J. P. Swazey, *Chlorpromazine in Psychiatry* (Cambridge, Mass,: MIT Press, 1974).

synthetic organic chemistry which in turn received a major impetus from the financial rewards of dye development. Since synthetic organic chemistry has been crucial in the development of modern biochemistry and most of biomedical research, we can see how monetary incentive has played a particularly prominent role in the most basic studies of the biology of living systems.

At the same time, the very basic studies of organic chemistry were crucial in permitting the synthesis of novel and more lucrative dyes. British firms at first were the leaders in the synthetic dye market. However, within twenty years they had lost their lead to the large German and Swiss companies. Most students of the field agree that the British dye industrialists failed to interact adequately with basic researchers in synthetic organic chemistry. Indeed, in 1910 the president of the British Society of Dyers and Colourists, Dr. F. Mendola, chastened his colleagues for their failure, "The question of the cause of the decline of the British Industry resolved . . . into the question of the cause of the continental activity . . . *which is research.* The decay of the British industry set in from the time when the continental factories allied themselves with pure science and the British manufactors neglected such aid."[2] It takes little imagination to perceive the relevance of Dr. Mendola's comments to our present academic-industrial relationships in biomedicine. In any event, the specific link of dyes to chlorpromazine is that the phenothiazine nucleus was synthesized in 1883 as a dye related somewhat to methylene blue.

Once phenothiazine itself was prepared, very little if anything was done with regard to its possible pharmacologic actions. The rest of the story of chlorpromazine relates to drugs which affect the body outside of the brain. While phenothiazine itself is a synthetic chemical, in one sense the true parent of chlorpromazine is the naturally occurring alkaloid atropine.

[2] Quoted in W. M. Gardner, *The British Coal-Tar Industry* (London: Williams and Norgate, 1915).

Atropine and Antihistamines. Atropine is the active ingredient of the belladonna plant. Belladonna had been used since antiquity for various medical purposes, almost all of which depended on its ability to block the actions of the neurotransmitter acetylcholine at various glands and muscles throughout the body. The interaction of acetylcholine with drugs provides an excellent example of both basic and applied science. Atropine had been isolated from the belladonna plant in 1837 and was used frequently by physiologists, because in the 1860's and 1970's researchers had observed that it could block various effects of nerve stimulation, especially of the nerves which acted upon certain glands. It had also become apparent in the late 1860's that atropine was useful in the treatment of Parkinson's disease. However, as often occurs in therapeutics, extensive efforts to develop drugs based on the atropine molecule did not take place until the fundamental mechanisms of its ability to block nervous activity had been worked out. This depended much on the work of Henry Dale.

Dale was an employee of the Burroughs Wellcome Drug Company and had been assigned the task of discovering commercially useful drugs from ergot. By 1914 he had already discovered that ergot contained substances which blocked the actions of adrenalin, discoveries foreshadowing a whole class of drugs which have been of great importance in clinical medicine, especially in treating high blood pressure. In 1914 he found that certain ergot extracts would lower the blood pressure of cats, an effect which was blocked by atropine. The nature of these effects reminded him of a finding by another pharmacologist, Reid Hunt,[3] that the blood pressure-lowering effects of adrenal extracts were attributable to a molecule which had first been synthesized in 1867 and had the chemical structure acetylcholine. Dale indeed was able to show that the hypotensive principle of the ergot was acetylcholine and that its actions were antagonized by atropine. Thus, he was the first to

[3] R. Hunt and R. de M. Taveau, On the physiological action of certain cholin derivatives and new methods for detecting cholin. *Brit. Med. J.,* 2: 1788–91 (1906).

discover that atropine exerted its pharmacological influences by specifically blocking the effects of acetylcholine.[4] Since the types of acetylcholine effects blocked by atropine resembled those produced by the alkaloid muscarine, these were referred to as muscarinic acetylcholine or "cholinergic" effects. Atropine was the first muscarinic anticholinergic drug. These findings stimulated research by numerous drug companies directed at developing newer atropine-like drugs.

Prompted by Dale's brilliant demonstration of naturally occurring adrenalin and acetylcholine blockers, the French chemist Fourneau began a long and systematic search for synthetic drugs that would block adrenalin and acetylcholine actions. Though some of his research synthesizing particular groups of compounds began as early as 1910, he reported no major successes until the 1930's, when a young Italian pharmacologist, Daniel Bovet, joined him. In 1933 Fourneau and Bovet found a chemical compound which did have potent and specific adrenalin-blocking activities. Bovet decided then to set out on a novel project of his own. With A. Staub, one of his doctoral students, he decided to evaluate new chemicals for their ability to prevent the actions of histamine as well as acetylcholine or adrenalin.

Why look for a drug that would block the actions of histamine? Here again, the role of basic science in a seemingly mundane "drug development" project is apparent. Bovet's effort to develop antihistamines was based on other pioneering work of Sir Henry Dale. While studying ergot extracts, Dale also had isolated histamine as a substance which contracted various smooth muscles and lowered blood pressure. These actions appeared virtually identical to those which occur during anaphylactic shock, a massive allergic reaction.[5] Though Bovet had no way of knowing how closely anaphylactic shock was related to most common

[4] H. H. Dale, The action of certain esters and ethers of choline and their relations to muscarine. *J. Pharmacol. Exp. Ther.,* 6:147–90 (1914).

[5] H. H. Dale and P. P. Laidlaw, The physiological action of beta-imidazolylethylamine. *J. Physiol.* (London), 41:318–44 (1910).

allergies, he apparently felt that a drug that could prevent anaphylaxis would be of interest.

In this research Bovet utilized a systematic screening approach which subsequently became standard in the drug industry. He set up tests both in intact animals and in isolated organ systems. By evaluating isolated tissues, he could directly examine the extent to which modifications in the chemical structure of a drug would influence its biological activity. Tests in intact animals suffer from the fact that one drug may be more potent than another simply because it is metabolized less or penetrates into a target organ more readily than the less potent derivative. Using isolated organ systems, one evaluates the primary site of action. The virtue of tests with intact animals, of course, is that if a drug is active, one then knows that it will not be totally metabolized and will reach the target organ.

Bovet utilized relatively simple screening tests — another important principle in drug development — to permit efficient evaluation of large numbers of test compounds. Injections of histamine in rather low doses kill guinea pigs. He simply tested drugs to see whether they would block the lethal effects of histamine injections. In guinea pigs histamine aerosols cause a massive asthma-like bronchoconstriction, which provides another simple screening test. Histamine contracts the isolated guinea pig intestine, which affords a simple isolated organ system. Bovet found some agents with fairly potent antihistaminic activity but which were also rather toxic. By 1939 he had begun to collaborate with the Rhone-Poulenc Drug Company, whose pharmacologist, Bernard Halpern, directed a program synthesizing analogs of Bovet's compounds. By 1942 the first commercially marketable antihistamine was developed and by 1944 the major antihistamines employed today had already been prepared. These include pyrilamine (Mepyramine, Neoantergan), diphenhydramine (Benadryl) and tripelennamine (Pyribenzamine).[6]

6 D. Bovet, Introduction to antihistamine agents and Antergan derivatives. *Ann. N. Y. Acad. Sci.,* 50:1089–1126 (1950).

For his work in developing antihistamines, Daniel Bovet shared the Nobel Prize in Medicine in 1957. It is interesting that virtually all the commercially employed antihistamines include among their major side effects atropine-like actions, a result of the fact that they were developed as descendants of the atropine molecule. The other major side effect of antihistamines is sedation, important because it ultimately led to the discovery of the antischizophrenic actions of neuroleptics.

The Revelation of Chlorpromazine. The Rhone-Poulenc Drug Company, having pioneered with the first commercially successful antihistamines, was eager to develop new agents of this class, especially ones that would lack the sedative side effects. Among the numerous chemical classes of antihistamines developed were the phenothiazines. Promethazine (Phenergan) was and continues to be one of the most potent of the phenothiazine antihistamines and is frequently used today. The story of the antischizophrenic neuroleptics, of which chlorpromazine was the first, begins with the suggestion that the sedative actions of antihistamines might have therapeutic utility. Credit for this notion goes to the French surgeon Henri Laborit.

Laborit was interested in the use of drugs as preanesthetic and postsurgical tools. He sought agents which might cause some sedation so that less anesthetic could be used subsequently. He also desired drugs which would block actions on the autonomic, involuntary nervous system, feeling that such effects might prevent shock. Agents to lower body temperature were of interest as well to reduce the metabolic requirements of the body. Over the years Laborit had developed a "cocktail" including barbiturates, morphine, curare (the nerve-muscle paralyzing agent), and local anesthetics such as procaine. The sedative, atropine-like, and hypothermic effects of promethazine intrigued him.

Seeking an even more sedating antihistamine than promethazine, Laborit contacted the Rhone-Poulenc Company and was given a sample of chlorpromazine. Chlorpromazine is a close chemical

derivative of promethazine but is more sedating and has substantially less antihistaminic activity. Laborit was most impressed with the effects of chlorpromazine, which he incorporated into his preanesthetic cocktail. He was also impressed with the ability of chlorpromazine to decrease the patient's anxious concern with his environment while not rendering the patient unconscious. Individuals treated with chlorpromazine seemed calm and detached from the outside world.[7] Laborit urged his psychiatric colleagues to try the drug in their patients. Numerous French psychiatrists experimented in an uncontrolled fashion with chlorpromazine in a variety of types of patients. During 1951 the breakthrough came with the extensive studies by Jean Delay and Pierre Deniker using a wide range of doses in a large number of patients.

Delay and Deniker administered chlorpromazine by itself, in contrast to some of the other initial trials in which chlorpromazine was used together with other drugs. Delay and Deniker had no way of knowing what types of patients might be affected by the drug. They "spread a wide net," investigating all sorts of doses and routes of administration in various types of patients. Of considerable importance is the fact that they gave progressively higher doses, whereas some of the initial researchers tried only small, largely ineffectual doses.

Their first major successes were in patients with various types of psychic excitement and agitation. Most of these individuals suffered from mania, a condition for which chlorpromazine continues to be an effective agent. Interestingly, the classic initial papers of Delay and Deniker did not emphasize the efficacy of the drug in schizophrenia. Thus, in one of their first publications they reported "Schizophrenia (6 cases): In this type of patient the relatively small number of treated cases and the brevity of the remission do not permit any estimate of the possible usefulness of the method in this most severe affliction. We have noticed only a

[7] H. Laborit, P. Huguenard, and R. Alluanume, Un nouveau stabilisateur vegetatif (le 456RP). *Presse Med.* 60:206–8 (1952).

few remissions, but several of them were among the particularly severe and refractory cases. The remarkable fact is that the signs in the catatonic series appeared to be very much helped."[8]

This rather modest endorsement of an effect of chlorpromazine in schizophrenia can be explained by the fact that severe, chronic schizophrenics are not likely to respond instantly and miraculously to any treatment. By contrast, the psychic and motor agitation of manics is alleviated by chlorpromazine in a matter of hours. Even after the introduction of chlorpromazine into psychiatry and its evaluation in schizophrenic patients, it was still several years before the psychiatric community appreciated the "main point," namely that a unique type of drug had been discovered which exerts a fundamental effect on the apparently primary abnormalities of schizophrenia.

The first publications indicating that chlorpromazine had unique efficacy in treating schizophrenia appeared in 1954.[9] Of 205 schizophrenic patients studied in Basel, Switzerland, chronic as well as acute and agitated patients responded. Severely and chronically withdrawn patients did well, just as did acutely agitated patients. In one of the early trials in the United States, in a state mental hospital in Ohio, Goldman came to similar conclusions: "chronic severe schizophrenic illness resistant to all other treatments has represented a 'therapeutic no-man's land'. The application of chlorpromazine in such situations has, however, accomplished results never heretofore achieved."[10]

Whether or not one feels that the introduction of chlorpromazine was largely serendipitous, it is clear that the multifaceted approach which resulted in its use tells us something about comparative aspects of undirected and mission-oriented research.

[8] Translated and quoted by Swazey, note 1 above, p. 136.

[9] F. Labhardt, Die Largactiltherapie bei Schizophrenien und anderen psychotischen Zustanden. Schweiz *Arch. Neurol. Psychiat.* 73: 309-38 (1954).

[10] D. Goldman, "The effect of chlorpromazine on severe mental and emotional disturbances," in *Chlorpromazine and Mental Health* (Philadelphia: Lea and Febiger, 1955), pp. 19-40.

Clearly, a targeted program to develop a drug for schizophrenia would not have resulted in chlorpromazine.

Molecular Approaches to Psychotropic Drugs

There has been much debate as to what, if any, lessons the chlorpromazine story teaches us about how to approach therapeutic innovation in medicine. Many drug companies use this tale as an argument for a virtually random route to drug development. They eschew molecular probes and any attempts to develop drugs based on fundamental mechanisms of action. Instead they argue that all one wants is some sort of "activity" in intact animals which will indicate that the drug will do *something* to humans. A wide range of screening tests are set up in small animals, usually rats. For instance, one can screen for an antiepileptic drug by measuring its ability to prevent convulsions induced by electroshock or other means. It is also likely that a drug which would prevent such seizures would have potential utility as a sedative, sleeping pill, or antianxiety agent.

According to this model of drug development, one need not have much interaction between chemists and pharmacologists. The task of the chemist simply is to produce large numbers of new patentable chemical entities. Since no one can predict just what chemical structure will be effective in treating various disease processes, the direction of synthesis is usually dictated by convenience. One follows a chemical route which can yield ten new structures in a week rather than a more complex synthesis which could provide only two or three compounds in several months. Chemicals which appear positive in some of the test systems are evaluated in more extensive procedures. Toxicology studies are conducted and drugs that seem safe and somewhat effective are then evaluated in humans.

One can raise many valid arguments in favor of this approach. The history of drug development is full of surprises. Drugs developed for one disease turn out to be useful for some com-

pletely unrelated condition. Chlorpromazine itself is an excellent example. The tricyclic antidepressant imipramine, prototype of almost all the major antidepressants used today, was synthesized as a chlorpromazine-like antischizophrenic drug. Its utility in treating depression was discovered only because the Swiss psychiatrist Roland Kuhn was persistent and thorough in his clinical trials, evaluating depressed as well as schizophrenic patients. The first monoamine oxidase inhibitor antidepressant, iproniazid, was developed as an analogue of the antituberculosis drug isoniazid. Astute clinicians noticed that the mood of the tuberculous patients was improved far more than could be accounted for simply by the reduction of their coughing and chest pain.

A wide-ranging "gross" screening strategy is also valuable when one does not know the mechanism whereby drugs might alleviate symptoms of a disease, much less the specific biochemical abnormalities which account for the symptoms. Even in cases where the biochemical actions of certain successful drugs are known, one could argue against developing other agents that act on the same biochemical mechanism. Such new drugs could be regarded only as "me too" agents, hence not genuine innovations. Why not screen at random for drugs so that one might encounter an agent that could relieve the same disability but by a completely new molecular mechanism?

On the other hand, if one does know the molecular site of action of certain successful drugs, agents which are more effective in exerting the same effect might well be valuable. Let us take the example of monoamine oxidase inhibitors. The means of measuring monoamine oxidase activity is quite straightforward so that one can screen new drugs in simple test tube systems. Thus one can evaluate the actual molar potency of new chemicals. In this way systematic structure-activity relationships can be worked out so that the chemist can efficiently move rapidly toward more and more potent chemicals. By using a screening test which does not require intact animals, more chemicals can be evaluated, as the

synthetic chemist may prepare only a few milligrams of the drug rather than the dozens of grams needed for screening tests in rats and larger animals. Very frequently, the toxic side effects of drugs are elicited at sites quite distinct from those that account for therapeutic effects. In this case, a drug which is extraordinarily potent at the therapeutic site can be employed in very low doses which are much less likely to elicit side effects.

In the case of the monoamine oxidase inhibitors, systematic studies over a reasonably brief period of time did result in agents with greatly enhanced potencies. Iproniazid has a hydrazine structure. Both iproniazid and other hydrazine monoamine oxidase inhibitors cause liver damage which in some instances is fatal. By straightforward screenings with purified monoamine oxidase preparations, scientists developed extremely potent monoamine oxidase inhibitors which do not incorporate the hydrazine moiety.

Besides providing for efficiency in drug development, molecular approaches may offer insight to fundamental abnormalities in the disease under question. Such insights sometimes give impetus to yet other ways of dealing with disease. The fact that monoamine oxidase inhibitors relieve the symptoms of depression suggests that the therapeutic actions of the drugs result from their augmenting the levels of monoamines in the brain. This thesis, based in large part on the existence of the monoamine oxidase inhibitor drugs, has been substantiated by a wide variety of pharmacological and biochemical evidence. Indeed, whole new classes of antidepressant drugs are being developed which facilitate the actions of the various monoamines in the brain by different mechanisms quite unrelated to inhibition of the enzyme monoamine oxidase. Thus, by exploring monoamine oxidase as a site of action of antidepressant drugs, one subsequently comes up with drugs which can relieve depression via rather different mechanisms.

In the area of psychoactive agents, monoamine oxidase was for many years the lone example of a rational approach to drug therapy. Until recently no one knew how the antischizophrenic neuro-

leptic drugs acted. The tricyclic antidepressants were widely used clinically before researchers were confident as to their mechanism of therapeutic action. The antianxiety benzodiazepine drugs were introduced in 1960, but almost twenty years passed before fundamental insights clarified their effects and how they act at a molecular level.

Much of our recent appreciation of how various psychoactive drugs act in the brain derives from the notion that they act on specific receptors which can be measured in a biochemical fashion. The receptors are proteins on the membranes of nerve cells in the brain whose normal function is to interact with neurotransmitters, the chemical messengers which mediate interactions between neurons and the brain. Let me explain some background briefly.

Neurons and Neurotransmitters. The brain contains several billion neurons or nerve cells. In the nineteenth century, microscopic examination of the brain revealed a massive network of nervous elements. Many scientists thought that this enormous tangle consisted of a single complex net, much like a giant spider web. For his anatomical studies indicating that the web involved billions of separate neurons connected to each other, Ramon y Cajal shared the Nobel Prize in 1906. Cajal also observed that each neuron consists of a cell body which sends out a long process or axon which in turn ramifies into hundreds or thousands of nerve endings, each of which can connect with a different neuron. Thus a single neuron can project its message forth to thousands of others. Closer to the cell body the neuron has processes called dendrites at which it receives information from hundreds or even thousands of other neurons. Clearly the opportunities for interaction of these billions of neurons are spectacularly large.

How is communication among these neurons mediated? Even in the nineteenth century scientists realized that neuronal functioning had electrical concomitants. Nerve impulses begin in the region of the cell body and proceed down the axon to the nerve ending electrically, much like the spread of impulse down an

electric wire. For many years researchers assumed that communication among neurons consisted of the electrical impulse "jumping" the gap, or synapse, between adjacent neurons. The Nobel Prize shared in 1936 by Otto Loewi and Sir Henry Dale was awarded for evidence the two of them had accumulated indicating that neurotransmission was at least in some instances chemical. It is now appreciated that almost all neurotransmission involves the release of neurotransmitters, though there are a few "electrical" synapses in the nervous system.

What is a neurotransmitter? It is a chemical generally synthesized in nerve endings from which it is released by the oncoming nerve impulse. At least thirty distinct neurotransmitters have been identified, and it is suspected that there may exist as many as 200 different ones. Each neurotransmitter can act only when it binds to a specific recognition site on the adjacent neuron. This recognition protein molecule is referred to as the neurotransmitter receptor.

The importance of neurotransmitters is that they represent the most efficient site for modulating nervous activity in the brain. The electrical transmission of an impulse from the cell body down the axon to the nerve ending is an all-or-none phenomenon. Chemical substances which interfere with this process are generally lethal and at best are not very specific in their actions. By contrast, one can alter the activities of various neurotransmitters in numerous, subtle ways. Virtually all known psychoactive agents exert their effects via interactions with one or another neurotransmitter. Drugs can alter the biosynthesis of the transmitter, change its release pattern, alter its metabolic destruction or its accumulation back into the nerve ending which released it. Alternatively, a drug can mimic or block the actions of a neurotransmitter at its receptor site. Drugs are known which act at each one of these synaptic sites. The greatest progress in recent years has related to drugs which act at receptors.

Althougth scientists have assumed for many years that neurotransmitters and drugs can act at specific receptors on neuronal membranes, such receptors remained hypothetical entities until the decade of the 1970's. Only in the past few years has it been possible to measure neurotransmitter and drug receptors at a molecular level. The ability to identify neurotransmitter and drug receptors in this way is one of the several revolutionary events in the brain sciences which have made this an area of rapid development in medicine.

The Opiate Receptor and Opiate-like Neurotransmitters. As I have said, one of the first known neurotransmitters was acetylcholine. It is a neurotransmitter at probably about five percent of the synapses of the mammalian brain. The first major success in measuring neurotransmitter receptors biochemically was not a result of experiments with the brain but rather with the electric organ of the electric eel and related invertebrates. These electric organs generate sufficient voltage to kill adult humans as well as other species which might attack the eel. All of this electrical activity is generated via mechanisms which involve acetylcholine synapses. Not surprisingly, the density of acetylcholine synapses in the electric organ is rather high. In *Torpedo marmerata,* one of the electric fishes, the acetylcholine receptor represents about twenty percent of membrane protein. By contrast, the density of acetylcholine receptors in mammalian brains is about one-millionth by weight of the brain. Utilizing a unique snake toxin which kills mammals by blocking acetylcholine receptors, several researchers were able to label these receptors by measuring the binding of radioactive forms of the toxin. It was generally assumed that such an approach was not likely to be feasible for most neurotransmitters in animal brains where there are so many fewer receptors and for which no extraordinarily potent, virtually irreversible toxin exists.

The ability to label neurotransmitter receptors in the mammalian brain turned out to be less difficult of achievement than

one would have thought. Indeed, unique, irreversibly binding agents were not required. Moreover, the very low number of such receptors in brain tissue was not nearly so insuperable a problem as most investigators had imagined. The first breakthrough did not deal with what was then thought to be a neurotransmitter receptor, but with the receptor for the opiate class of drugs.

The opiates, including morphine, heroin, codeine, and many synthetic agents, are among the oldest known drugs. Though researchers have searched for years, they have never discovered any substances that can relieve severe pain as effectively as can the opiates. Besides their importance as analgesics, the opiates are the prototype of addictive agents. Tolerance and physical dependence to opiates is analogous in its formal properties to addiction which occurs to other classes of drugs including alcohol, barbiturates, amphetamines, cocaine, and antianxiety drugs such as Valium. Molecular mechanisms of opiate addiction might well be closely mirrored with other types of drugs.

For all of these reasons researchers were eager to find out how opiates exert their actions. Pharmacologists had given animals opiates and measured levels of various neurotransmitters as well as protein, carbohydrate, and lipid disposition. Opiates affect many biochemical processes in the body. How is one to determine which of these account for the pharmacological actions of the drugs? Based on fairly simple pharmacological grounds, one could postulate that opiates probably exert their actions at highly specific receptor sites. If one could measure those receptor sites and knew exactly which neurons in the brain possess them, then one could identify the sites of primary action of the drugs.

The approach taken in our own and other laboratories was simply to measure the binding of radioactive opiates to brain membranes.[11] We were concerned that the opiates might bind in a nonspecific fashion to many membrane molecules other than the

[11] S. H. Snyder, "Opiate receptors and opioid peptides," in *Harvey Lectures* (New York: Academic Press, 1979), pp. 291–314.

very few opiate receptors. To hone in selectively on the opiate receptors we used low concentrations of the radioactive opiate which bound preferentially to the receptors rather than to nonspecific sites. Binding to nonspecific sites was circumvented by washing brain membranes thoroughly after incubating them with the radioactive opiates. The binding sites thus identified interacted with different drugs in proportion to their ability to mimic the pharmacological actions of morphine.

A number of dramatic properties of the opiate receptor soon became apparent which had fundamental as well as practical ramifications. The opiate receptor is regulated by sodium ions in a unique fashion. Drugs which mimic the effects of morphine, called agonists, become weaker in binding to the opiate receptor in the presence of sodium. There also exist opiate antagonists, which are drugs that can bind to the opiate receptor but which do not elicit any morphine-like actions themselves. Instead, by occupying opiate receptors they prevent access of morphine and related agents and so are referred to as opiate antagonists. The binding of "pure" opiate antagonists to the opiate receptor is not diminished by sodium ions. Drugs with both agonist and antagonist activities are affected in an intermediate fashion.

It was already known that opiates with both agonist and antagonist activity tend to be less addictive than pure agonists such as morphine. Indeed, many drug companies were engaged heavily in attempts to develop such mixed agonist-antagonists as less addicting analgesics. Screening tests for this class of drug in intact animals were difficult and tended often to provide unreliable results. A simple test tube system to measure the effect of sodium on the ability of the drug to interact with opiate receptors offered great advantages. Today, measuring opiate receptor interactions and the influence of sodium and related substances that help differentiate agonists and antagonists is a routine activity in most major pharmaceutical concerns.[12]

[12] W. Zieglgansberger and H. Bayerl, The mechanism of inhibition of neuronal activity by opiates in the spinal cord of the cat. *Brain Res., 115* :111–28 (1976)

The influence of sodium on the opiate receptor had implications for some fundamental aspects of nervous system function. When a neurotransmitter interacts with its receptor, it either excites or inhibits cellular firing. These changes in neuronal functioning generally involve an opening or closing of certain ion channels in the neuronal membrane. Somehow, recognition of the neurotransmitter at its receptor site triggers these alterations in ion channels. The ion channels are thought to be closely linked to the recognition portion of the receptors and may in fact be part of the same macromolecular complex. The influence of sodium on opiate receptor function suggested that sodium might be an ion crucially involved in opiate-induced alterations in cellular function. Subsequent studies did show that sodium is important for the ability of opiates to affect the firing of neurons and cellular changes in cyclic AMP (adenosine monophosphate).

Opiate receptor research also opened new vistas for neurophysiologists and neuroanatomists who had been attempting for many years to elucidate how the nervous system processes information about pain. Techniques were developed which permitted visualization of opiate receptors at a microscopic level. These studies showed that opiate receptors were not homogenously distributed throughout the nervous system. Instead they occurred in very specific, discrete localizations. Many of these localizations involved sites which had been suspected for years to be involved in integrating information about pain perception. Localization of opiate receptors at other sites in the brain could explain how opiates exert many of their pharmacological effects besides relief of pain. For instance, death from overdose of opiates usually occurs by depression of respiration. One of the nuclei in the brain, the nucleus of the solitary tract, which has a very high concentration of opiate receptors, is crucially involved in some of the reflex mechanisms that regulate respiration. Neurosurgeons have shown that electrical stimulation in some of the areas rich in opiate receptors relieves pain. Such stimulation is now employed as a

therapeutic technique in some cancer patients with intractable pain. Thus, by revealing fundamental aspects concerning brain areas involved in pain perception, discovery of the opiate receptor has provided new ways of treating pain quite apart from providing a technique for the simple screening of drugs for their effects on the opiate receptor. This situation is analogous with that described earlier for monoamine oxidase, monoamine potentiation, and depression.

A further example of this cycle of basic findings and therapeutic application in both direct and indirect ways is apparent as well in the study of endogenous morphine-like molecules. The dramatic properties of the opiate receptors suggested that they must have some function other than dealing with exogenous drugs. Could they be receptors for a normally occurring morphine-like neurotransmitter? John Hughes and Hans Kosterlitz in Scotland[13] and then Rabi Simantov and I in Baltimore[14] succeeded in identifying two small peptide molecules which indeed are the brain's own morphine-like neurotransmitters. They are referred to as the enkephalins. With staining techniques employing antibodies to the enkephalins, it was possible to map the location of the enkephalin neurons throughout the brain. The enkephalins are contained in both short and long neurons which tend to be localized to the same parts of the brain as the opiate receptors. Since the enkephalins are composed of only five amino acids, it is fairly simple for chemists to devise novel structures which might mimic the enkephalins. Thousands of such enkephalin analogues have been developed as potential drugs. As yet no commercially marketed enkephalin analogues have appeared, but promising agents are being evaluated.

[13] J. Hughes, T. W. Smith, H. W. Kosterlitz, L. Fothergill, B. A. Morgan, and H. R. Morris, Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature 258*: 577-79 (1975).

[14] R. Simantov, and S. H. Snyder, Morphine-like factors in mammalian brain: structure elucidation and interactions with opiate receptor. *Proc. Natl. Acad. Sci., U.S.A., 73* :2515–19 (1976).

After release by neurons, all neurotransmitters must be inactivated so that the receiving neuron can then interact with a new burst of neurotransmitter release. The body possesses numerous enzymes, called peptidases, which can degrade peptides. Researchers have been searching for peptidases which might be specific for enkephalin. Though several enzymes have been described which have "enkephalinase" activity, it is not certain yet as to which if any of them are selectively associated with enkephalin synapses and opiate receptors. However, drug companies are searching already for compounds capable of inhibiting enkephalinase activity. If one prevents enkephalin degradation, then brain levels of enkephalin should rise. Presumably analgesia and other typical opiate-like effects would ensue. It is conceivable that gradually increasing brain levels of the normally occurring morphine-like neurotransmitter would be a better way of dealing with pain than bombarding opiate receptors with synthetic molecules. Inhibitors of enkephalinase are only beginning to be tested in animals; however, there is evidence already that useful pharmacologic and possibly therapeutic effects can be obtained. Besides possible practical applications, understanding mechanisms whereby a peptide neurotransmitter is metabolized should aid considerably in our attempts to elucidate just how neurotransmitters function.

The first neurotransmitters identified, acetylcholine and norepinephrine, were in the chemical class of amines — carbon-containing molecules which possess a nitrogen linked to hydrogens. By contrast, the enkephalins are peptides — amino acids linked to each other as in proteins. Indeed, peptides can be regarded merely as very short protein molecules or proteins as very long peptides. The discovery of the enkephalins focused attention on the concept of peptides as neurotransmitters. There was already evidence that some peptides, such as Substance P, might be neurotransmitters. The very extensive and widely appreciated information about the enkephalins spurred new interest in peptides in the brain. Subsequently, there has been a rash of dis-

coveries of peptide neurotransmitters.[15] We already know the existence of about two dozen. Considering the sometimes serendipitous ways in which the peptides are discovered, it is quite conceivable that another 100-200 peptide transmitters await discovery. Every one of the new brain peptides has properties which are just as interesting as those of the enkephalins. The challenge of future years is to examine the brain systematically to try to uncover more of the peptide transmitters. At the same time, one must characterize the properties of each of them in great detail. Each of these peptides is an excellent candidate for drug development. One can look for drugs that will mimic the effects of a peptide, block its actions, alter its synthesis or metabolism. In a sense, much of the new research on brain peptides stems from discovery of the opiate receptor. Here again, we see the extraordinary range of basic and applied advances that can derive from a few fundamental observations in biology.

The principles which made possible the monitoring of opiate receptor binding were soon applied to the known neurotransmitters in the brain. One could measure the binding of the neurotransmitter itself or of drugs which were neurotransmitter agonists or antagonists. In this way it has now been possible to measure receptors for most of the known neurotransmitters in the brain. There have been both fundamental and applied findings.

Dopamine Receptors Mediate Antischizophrenic Actions of Neuroleptics. The ability to measure receptors for the neurotransmitter dopamine has had a bearing on the understanding of how the antischizophrenic neuroleptic drugs act. A variety of indirect evidence accumulated over the years had suggested a role for dopamine in the actions of the neuroleptic drugs. The great success of chlorpromazine had prompted efforts by the drug industry which resulted in the marketing of many neuroleptic agents. Thus, one could monitor biochemical actions of a series of neuro-

[15] S. H. Snyder, Brain peptides as neurotransmitters. *Science*, 209:976–83 (1980).

leptics including potent, weak, and inactive drugs. Biochemical effects which were exerted by neuroleptics in accordance with the therapeutic potencies would signal good candidates for the sites of therapeutic actions of the drugs.

While neuroleptics affect several neurotransmitter systems in the brain, changes in brain levels of breakdown products of dopamine tended to fit best with therapeutic potencies of the drugs. Because these studies were done in intact animals and only limited numbers of drugs could be evaluated, it was not clear just how well these effects did fit with therapeutic actions. Moreover, it was not at all evident just what the changes in metabolic patterns of dopamine implied. The Swedish pharmacologist Arvid Carlsson had suggested in a preliminary fashion that blockade of dopamine receptors followed by a series of feedback effects on dopamine neuronal firing could be responsible.[16]

This conjecture could not be tested until one could measure dopamine receptors. When we[17,18] and Seeman[19] were able to monitor dopamine receptors based on the same principles that permitted measurement of opiate receptors, we could test Carlsson's hypothesis directly. In a large series of drugs, relative potencies in blocking dopamine receptors did indeed predict the therapeutic activities of the drugs. [20, 21] However, neuroleptics can affect other

[16] A. Carlsson and J. Lindqvist, Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta. Pharmacol. Toxicol,* 20: 140–44 (1963).

[17] D. R. Burt, S. Enna, I. Creese, and S. H. Snyder, Dopamine receptor binding in the corpus striatum of mammalian brain. *Proc. Natl. Acad. Sci., U.S.A.*, 172:4655–59 (1975).

[18] I. Creese, D. R. Burt, and S. H. Snyder, Dopamine receptor binding: differentiation of agonist and antagonist states with [3H] dopamine and [3H] haloperidol. *Life Sci.,* 17:993–1002 (1975).

[19] P. Seeman, M. Chau-Wang, J. Tedesco, and K. Wang, Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proc. Natl. Acad. Sci., U.S.A.,* 72:4376–80 (1975).

[20] I. Creese, D. R. Burt, and S. H. Snyder, Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science, 192:48l–83 (1976)

[21] P. Seeman, T. Lee, M. Chau-Wang, and K. Wong, Antipsychotic drug doses and neuroleptic dopamine receptors. *Nature*, 261:717-19 (1976).

receptors. Recently, we measured effects of a large number of neuroleptics at receptors for several other neurotransmitters. Though neuroleptics were sometimes as potent at other receptors as at dopamine receptors, there was never a significant correlation between potencies of the drugs in blocking other receptors and their antischizophrenic activities.[22]

Interestingly, however, we showed that effects of neuroleptics at other receptors could explain many of the side effects of the drugs. One of the major side effects of neuroleptics involves difficulty in movement which resembles the symptoms of patients with Parkinson's disease. It is well established that Parkinson's disease is caused by a degeneration of a particular group of dopamine neurons which project into the corpus striatum, a brain region concerned with the regulation of bodily motion. By blocking dopamine receptors in the corpus striatum, the neuroleptics produce a functional equivalent of Parkinson's disease. The corpus striatum also contains a high concentration of acetylcholine neurons. As I have mentioned, atropine and related drugs that block muscarinic acetylcholine receptors alleviate the symptoms of Parkinson's disease. As I have also discussed, the phenothiazine neuroleptics were developed through a systematic series of chemical modifications beginning with the atropine molecule. Thus, most phenothiazine neuroleptics have varying degrees of atropine-like activity. We hypothesized that the neuroleptics which exert fewer of these Parkinson's disease-like side effects might do so because they block acetylcholine as well as dopamine receptors. Indeed, we did show that the neuroleptics which exerted fewer of these side effects were more potent at blocking these acetylcholine receptors.[23] These studies were made possible because we had

[22] S. J. Peroutka and S. H. Snyder, Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic and histamine receptors to clinical potency. *Am. J. Psychiat.,* 137:1518–22 (1980).

[23] S. H. Snyder, D. Greenberg, and H. I. Yamamura, Antischizophrenic drugs and brain cholinergic receptors. *Arch. Gen. Psychiat.,* 31: 58–61 (1964).

developed procedures enabling us to measure the binding of the appropriate radioactive drugs to muscarinic acetylcholine receptors.

In other studies we showed that the tendencies of various neuroleptics to cause sedation could be predicted by their ability to block the alpha forms of norepinephrine receptors in the brain, receptors which could be measured by binding techniques with appropriate drugs.[24] Thus both sedative and Parkinson's disease-like side effects of neuroleptics could be predicted by simple test tube binding experiments. At the same time, the antischizophrenic actions could be monitored in binding assays of dopamine receptors.

Characterization of dopamine, norepinephrine, and acetylcholine receptors in the brain has aided greatly in the understanding at a basic level of how these neurotransmitters function. The work with dopamine receptors has formed part of a "dopamine hypothesis" suggesting that dopamine may play a role in the genesis of some of the symptoms of schizophrenia. This hypothesis has not been proven by direct studies of biochemical properties of the schizophrenic brain; however, the notion has provoked a great amount of basic research into the biochemistry of schizophrenia and other forms of mental illness.

A New Collaboration Between Basic Biomedical Science and Industry?

Surely, for many years the drug industry was reasonably well justified in paying scant attention to what was going on in university laboratories. The system of synthesizing many chemicals and screening them in intact animals had produced many therapeutic breakthroughs. Very few therapeutic advances, especially at the level of new drugs, emerged directly or indirectly from

[24] S. J. Peroutka, D. C. U'Prichard, D. A. Greenberg, and S. H. Snyder, Neuroleptic drug interactions with norepinephrine alpha-receptor binding sites in rat brain. *Neuropharmacology,* 16:549–56 (1977).

university laboratories. It is the thesis of this essay that recent advances in biomedical research call for a reexamination of the university-industrial relationships. Though the examples I have given deal only with psychotropic drugs, they apply just as well to drugs in all branches of medicine and to non-drug therapy as well. Not only do new scientific findings permit more effective screening of drugs, but the drugs themselves serve as valuable probes of biological systems. Thus, while industry is indebted to the university for some of the basic findings, these same findings would not have been possible without the use of the drugs as probes of the body's biochemistry. Without opiates that could be synthesized in a radioactive form, the opiate receptor and the enkephalins would never have been discovered.

Of course, the drug industry is certainly aware of the utility of certain basic scientific findings, such as neurotransmitter receptors. This is evident in the fact that receptor binding procedures have been extensively adopted throughout the drug industry. However, I suspect that neither university nor industry has adequately thought through the implications of the new biology for future developments. I have provided examples of how cycles of applied and basic science feed back on one another. The rate of these reciprocal developments is becoming more and more rapid. In the past one could argue that the universities should do basic research and that industry should exploit their findings for therapeutic and commercial applications. Now, I would argue that industry must itself become directly involved in the process of fundamental, undirected, non-mission-oriented research. Though this already takes place on a limited scale, I would argue that such involvement should be expanded by an extent measured in orders of magnitude. Perhaps it would not be necessary for drug companies to have "in-house" large basic research laboratories. It may be possible to forge close and reciprocal scientific and fiscal links between university and industry.

The goals of such an endeavor are manifold. Development of new therapeutic agents would be facilitated. I feel that basic scientists in universities would benefit in their fundamental research from the tools afforded by industry. Every drug company has a store of thousands of chemicals which could be invaluable probes in characterizing all sorts of biological systems. Tapping these vast storehouses of chemicals would both accelerate the process of basic discovery and in turn feed back to the drug industry in new, hitherto unsuspected, therapeutic agents. Finally, at a time when governmental support of basic scientific research is becoming increasingly tenuous, industry might serve mankind by preventing the loss of a generation of scientific endeavor.