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The clinical investigator: bewitched, bothered, and bewildered--but still beloved.

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Editorial

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Editor's note: It is a difficult time for “physician-scientists.” The increasing specialization of science on one hand and the financial demands of managed care on the other are forcing a reconsideration of the role and importance of these individuals. Are they a dying breed? Or are they merely being redefined? In this editorial, Joseph Goldstein and Michael Brown of the University of Texas Southwestern Medical Center in Dallas describe their reading of the plight of the physician-scientist, and offer a suggestion how this beleaguered species might be saved.

We plan to continue this discussion in the pages of *JCI* in the future, because of its interest to our readers and its critical importance to the future of the American Society for Clinical Investigation. We welcome your responses and observations, some of which we will publish in a new section of “Letters to the Editor.” Send your written thoughts to: *Letters to the Editor, Journal of Clinical Investigation, P.O. Box 131220, Ann Arbor, MI 48113-1220.*

For the past 50 years, clinical departments in American medical schools have maintained a vision of the physician-scientist as a broad-based investigator who discovers fundamental biological mechanisms and applies these insights directly to the cure of disease. The success of this model can be traced to the vision of one man, James Shannon (1904–94), the father of the modern National Institutes of Health (NIH) and the creator of our nation's biomedical research enterprise. As director of the NIH in the 1950s and 1960s, Shannon postulated that diseases will be cured only when science provides a fundamental understanding of physiology, both normal and deranged. He transmitted this world view to political leaders, thus triggering the enormous postwar growth of basic science departments at the NIH and at the nation's medical schools. To apply this research to disease, Shannon envisioned a cadre of physician-scientists who would translate discoveries to the bedside.

Shannon's model produced a breathtaking revolution in biology, the clinical implications of which are just beginning to be tapped. Yet, paradoxically at the very height of its success, this

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model is threatened. The threat comes not from the basic side. To the contrary, basic research is flourishing as never before. Rather, the threat comes from the failure of the cadre of physician-scientists to grow in proportion to the numbers in basic research. Indeed, this cadre is shrinking as young physicians are forced to choose between performing research or practicing medicine, but not both. In this article we highlight both the achievements and challenges faced by the physician-scientist, and we propose steps that may solve some of the problems. We begin with a consideration of Shannon's multifaceted career, which exemplifies the highest aspirations of his model.

A compartmentalized career in biomedical science

Shannon's career comprised four distinct phases, separated in time and place: (1) pure basic research conducted at New York University School of Medicine (1931–41); (2) patient-oriented research (POR)¹ at the Goldwater Memorial Hospital (1941–46); (3) drug development at the Squibb Institute of Medical Research (1946–49); and (4) research administration at the NIH (1949–68).

As a basic scientist, earning a Ph.D. after receiving his M.D., Shannon discovered the fundamental mechanisms by which the kidney concentrates and eliminates solutes such as urea and creatinine. His classic studies are still described in physiology textbooks. When World War II began Shannon turned to POR, directing a 100-bed clinical research unit at Goldwater Memorial Hospital that evaluated new antimalarial drugs. This was classic clinical research, requiring direct patient contact and collaboration with academic physiologists and biochemists as well as with scientists from pharmaceutical companies. When World War II ended, Shannon turned to drug development, becoming Director of the Squibb Institute of Medical Research. Here he oversaw the development and marketing of streptomycin, the first antibiotic effective against tuberculosis (1–3).

In 1949, Shannon joined the newly created NIH as its first Associate Director in charge of research in the brand-new National Heart Institute, now the National Heart, Lung, and Blood Institute (NHLBI). His first job was to recruit a scientific staff. This was not easy 50 yr ago. What respectable scientist wanted to move to a backwater place like Bethesda, Maryland to do science in a federal bureaucracy? Nevertheless, within 3 yr Shannon filled the Heart Institute with a remarkable mixture of Ph.D.'s and M.D.'s, including three future Nobel laureates (Christian Anfinsen, Julius Axelrod, and Martin Rodbell), two future directors of the NIH (Donald S. Fred-

1. *Abbreviations used in this paper:* AAP, Association of American Physicians; AFMR, American Federation for Medical Research; ASCI, American Society for Clinical Investigation; DOR, disease-oriented research; HHMI, Howard Hughes Medical Institute; PAIDS, paralyzed academic investigator's disease syndrome; POR, patient-oriented research.

rickson and James B. Wyngaarden), and 13 future members of the U.S. National Academy of Sciences.

In 1955, Shannon was appointed Director of the entire NIH, a position from which he engineered the enormous growth of the biomedical research enterprise, both at the Bethesda campus and in research institutes, universities, and medical schools throughout the country.

From the standpoint of the physician-scientist, Shannon's career provides a clear lesson: One can be all things to all people, but not at the same time. We return to this essential point later.

The rise and fall of ASCI and AAP

The problems faced by the Shannon model are reflected by the problems of the two honorific societies for clinical investigation in the U.S.—the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP). Founded by physicians devoted to mechanism-based research, these societies elect physicians based primarily on their research achievements. In the Shannon era these societies dominated clinical research, and their annual meetings were a celebration of discoveries across the entire spectrum of disease. Shannon was an active member of these societies for 50 yr, and he received their highest honors (3).

Fig. 1 shows the attendance from 1978 to 1996 at the joint annual meetings of the ASCI, AAP, and the American Federation for Medical Research (AFMR), a sister society for younger clinical investigators. The number was fairly constant (~3,600) between 1978 and 1990, but then it declined dramatically, falling to 1,662 in 1996. If the downward trend continues at the same rate, attendance will drop to zero after year 2000—a new Millennium for the ASCI/AAP/AFMR!

What are the reasons for this precipitous decline? Does it signify the demise of the Shannon model? In 1977, James B. Wyngaarden, who was later to become director of the NIH (1982–89), was the first to express concern publicly about the declining interest of physicians in clinical research. In his often-quoted remarks, he referred to M.D. investigators as an “endangered species” (4). Wyngaarden's concern was based on an analysis of NIH grant applications, which revealed a striking

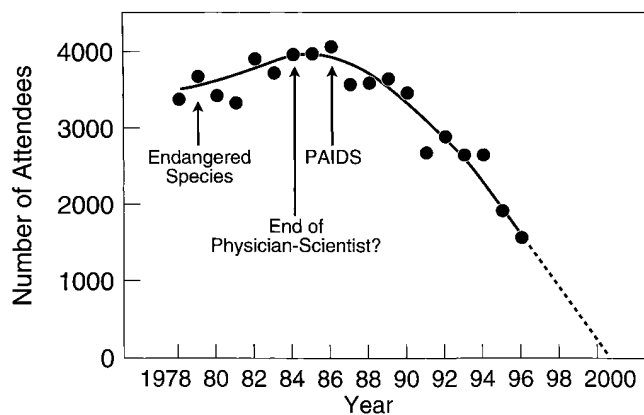


Figure 1. Attendance at annual meetings of ASCI/AAP/AFMR. The decline was anticipated in 1979 by James B. Wyngaarden (“Clinical Investigation as an Endangered Species”), in 1984 by Gordon N. Gill (“The End of the Physician-Scientist?”), and in 1986 by Joseph L. Goldstein (“On the Origin and Prevention of PAIDS—Paralyzed Academic Investigator’s Syndrome”).

decline in the number of M.D. applicants at a time when the number of Ph.D. applicants was increasing rapidly.

In 1984, Gordon Gill published a provocative article with a question for its title: “The End of the Physician-Scientist?” He pointed out that many research-oriented physicians had been seduced by the power of molecular biology and had abandoned POR (5). In a well-chosen illustration, he stated that the most creative M.D.’s prefer to present their data in meetings at Cold Spring Harbor, the spa of the basic scientists, rather than at the Washington Sheraton, the annual shrine of the ASCI/AAP/AFMR.

In 1986, one of us (J.L. Goldstein), developed this concern further by pointing out that the movement of scientifically trained M.D.’s toward basic research created a vacuum in clinical research that was often filled by M.D.’s who lacked fundamental research skills. Goldstein offered a new diagnosis for this malady; he called it “PAIDS” for Paralyzed Academic Investigator’s Disease Syndrome (6). M.D.’s with PAIDS are unable to solve biological problems because they lack the basic science training necessary to creatively use new approaches and techniques. Goldstein traced the pathogenesis of PAIDS to a simple phenomenon: the rapid pace of contemporary research makes it extremely difficult, if not impossible, for one person to be an intense clinician and an intense researcher at the same time. He challenged the appropriateness of the model of the physician-scientist who sees patients in the morning and clones genes in the afternoon. On rare and exemplary occasions this model is successful, but too often it predisposes to PAIDS. Faced with the necessity to choose between basic science and clinical research, most scientifically trained M.D.’s are choosing basic science.

Why have M.D.’s gravitated to basic science? One reason is that ordinary basic research is easier to perform successfully than is clinical research. A basic scientist can choose a project without constraint, selecting a problem that is ripe for solution because new tools are at hand or because another scientist has made a discovery that breaks an experimental logjam. Once such a breakthrough has been made, it is relatively easy to anticipate the next experiment and to perform it. This type of basic science, although not revolutionary, nevertheless produces definitive results that are intellectually satisfying. These results can be published in respected journals and will qualify for NIH funding.

In recent years the pace of basic research has accelerated as a result of technological breakthroughs that produce renewable reagents, easily obtained by any scientist who wishes to do the next experiment in a field. These include cDNA clones, proteins produced from recombinant DNA, and monoclonal antibodies. Innumerable companies now supply these biologic materials as well as premixed chemicals and kits that make experiments easy to perform without a deep technical background. To the individual scientist, the rapid dissemination of research tools is good news and bad news. The good news is that you can do lots of experiments. The bad news is that your competitors can also do lots of experiments. This threat increases the pressure to work intensely to stay ahead of the pack, and this in turn renders the dual research/clinical career increasingly difficult.

Basic science proceeds by way of abstraction, focusing on fundamental properties of living systems. The complexities of integrated organs and organ systems, especially if deranged by disease, are deliberately sheared away, and fundamental prop-



Figure 2. *L'Inventive collective* (*The Collective Invention*). René Magritte, 1930. © 1997 C. Herscovici, Brussels/Artists Rights Society (ARS), New York.

erties are revealed. By contrast, the complex world of disease is deliberately the focus of the clinical scientist (7). Clinical scientists lack the freedom to choose their targets. They must play the hand that nature has dealt them. The rheumatologist works on rheumatoid arthritis not because it is soluble but because patients are suffering. Non-insulin-dependent diabetes mellitus is “a geneticist’s nightmare,” yet its solution is imperative. Rarely can clinical scientists solve problems like these with the certainty that basic science provides. Clear-cut results are difficult to achieve, and this invites conflicting conclusions and controversy. Under such circumstances it is easy to see why NIH funding for clinical research is so often out of reach.

Clinical research is also made more difficult by the increasingly stringent demands of managed care and federal health insurance programs. These programs demand the constant physical presence of the physician, thereby precluding the performance of basic science and the supervision of patient care at the same time.

The beleaguered individuals who continue to combine basic science and clinical medicine often feel like the chimeric creature in the painting by the famous surrealist René Magritte (Fig. 2). Half human, half fish—they are not at home on land or in the sea.

Is the decline of the physician-scientist irreversible? We think not. Opportunities for creativity are greater than ever before. The basic scientists have provided the tools that will allow a rapid unraveling of our most frustrating diseases. But to take advantage of this opportunity, the Shannon model must be modified so as to allow physician-scientists to perform narrower, more focused roles. Breadth will be attained by collaboration between specialists rather than through comprehensive performance by individuals. This change is already occurring, as reflected by the attendance record at another research society, the American Society for Human Genetics (ASHG) (Fig. 3). In striking contrast to the ASCI/AAP/AFMR, the ASHG has witnessed a large increase in attendance. A similar increase has been noted at other speciality societies, such as the Endocrine Society, American Society of Hematology, American Gastroenterology Association, and others (8).

Why are the general, multidisciplinary societies languishing, while the specialty societies are booming? One answer lies in the disappearance of the medical science generalist. In their glory days the ASCI and AAP drew strength from strong departments of internal medicine that functioned as coherent

units that encompassed all aspects of the discipline. These broad-based departments have been replaced by loose confederations of specialty groups, each focused on a single discipline such as cardiology, gastroenterology, or genetics. Members of these groups focus their attention on a single organ, and usually just a portion of that organ. Thus, the scope of physician-scientists is further narrowed. Not only must they abandon the idea of being both physicians and scientists; they must also restrict their focus to a subset of organs and diseases. In the words of Lloyd H. Smith, Jr., the medical generalist is like a fox who knows many things, while the medical subspecialist is like a hedgehog who knows one big thing (8).

Three research careers open to M.D.’s

The research-oriented M.D. who has just completed clinical training can pursue three different types of research: basic research, disease-oriented research (DOR), and POR. The first two avenues are open to Ph.D.’s as well as to M.D.’s. The third avenue is largely, though not completely, restricted to M.D.’s. The distinction between DOR and POR is crucial because basic research and DOR are flourishing, while POR is falling behind. We define DOR as research that is targeted toward the understanding of the pathogenesis or treatment of a disease,

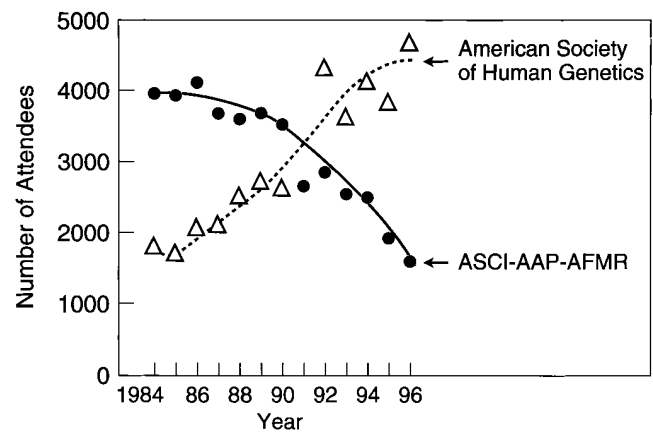


Figure 3. Changing trends in clinical investigation as reflected by comparison of attendance at annual meetings of ASCI/AAP/AFMR (filled circles) and American Society of Human Genetics (open triangles).

but does not require direct contact between the patient and the scientist. It may use patient materials such as cultured cells or DNA samples, but not the whole patient. In contrast, POR is performed by physicians who observe, analyze, and manage individual patients. As a rule of thumb, if the investigator shakes hands with the patient in the course of the research, that scientist is performing POR.

Below we present a few selected examples of clinically trained M.D. scientists whose discoveries epitomize the three categories of research described above. We emphasize that these are only a few examples selected from hundreds that are equally noteworthy.

Pure basic research. Many eminent scientists, including Nobel laureates Arthur Kornberg (DNA polymerase), Francois Jacob (*lac* operon), and Daniel Nathans (restriction enzyme mapping of genes), were clinically trained physicians who moved to basic research. All three performed internships/residencies in medicine or surgery, yet they chose research topics that responded to the challenges of pure fundamental science. Their revolutionary discoveries changed the ways in which biologists look at the world.

DOR. Karl Landsteiner, Rudolph Schoenheimer, and Oswald Avery are three historic individuals who conducted DOR. Having been stimulated by a particular disease, they pursued courses that took them away from patients, but they maintained their focus on disease.

Stimulated by the clinical problem of massive hemolysis after blood transfusions, Karl Landsteiner (1868–1943) discovered the A, B, O blood groups and advanced the theory of chemical immunity, thereby establishing the science of immunogenetics (6).

Stimulated by a patient with hypercholesterolemia, Rudolph Schoenheimer (1898–1941) hit upon a new way to quantify the fluxes of cholesterol and other metabolites in whole animals (6, 9). He conceived the idea of using isotopes as molecular tracers for biochemical events and made the surprising discovery that complex molecules, such as cholesterol, triglycerides, and proteins, constantly turn over in the body as a result of continual synthesis and degradation. His description of the dynamic state of body constituents transformed physiology in the 1930s and 1940s much as recombinant DNA transformed genetics in the 1970s and 1980s.

Stimulated by patients with pneumococcal pneumonia, Oswald Avery (1887–1955), a practicing physician, studied the mechanism by which an avirulent strain of pneumococcus was transformed into a virulent one. The result was the discovery that genes are made of DNA (10).

Each of these scientists used his medical background to derive the stimulus, breadth, and flexibility to unify a range of empirical observations into a powerful biomedical discovery. By our current definition, these three M.D.'s began their careers doing POR, but their research became more and more basic until it no longer depended on patients. By this time it had become DOR.

In a more personal and less epochal way, our own collaborative research over the last 25 yr likewise moved from POR to DOR. Our initial work on the receptor-mediated control of cholesterol metabolism (11) was directly stimulated by caring for a 6-yr-old girl with homozygous familial hypercholesterolemia (FH) who had extensive cutaneous xanthomas and advanced coronary atherosclerosis, owing to a markedly elevated level of plasma LDL-cholesterol. This patient had been hospi-

Table I. Some Physicians Who Perform DOR

Physician-Scientist	Field of exploration
Michael Bishop and Harold Varmus	Oncogenes
Francis Collins	Positional cloning of disease genes
*Y.W. Kan	Restriction-fragment polymorphisms
*Robert Lefkowitz	G protein-coupled receptors
*Stuart Orkin	Globin gene transcription
Stanley Prusiner	Prions and neurodegenerative disease
Janet Rowley	Cancer cytogenetics
*Bert Vogelstein	p53 mutations, cell cycle, and cancer

*HHMI investigators.

talized in 1968 at the NIH Clinical Center under the care of Donald S. Fredrickson, whose pioneering POR led to the classification of patients with inherited forms of hyperlipoproteinemia (12). When we encountered this patient, we were both clinical associates at the NIH, having just completed internships and residencies in medicine at the Massachusetts General Hospital. After we moved to Dallas, we determined to unravel the underlying defect in the 6-yr-old girl and others with FH. Our approach, unorthodox at the time, was to compare the regulation of cholesterol metabolism in a nonhepatic cell (i.e., the cultured fibroblast) from normal subjects and from patients with homozygous FH. These studies led to the discovery of the LDL receptor, which provided a glimpse into the general biological process of receptor-mediated endocytosis (13). Today, we have returned to the problem of cholesterol-mediated feedback regulation and are studying how cells use a family of novel membrane-bound transcription factors (SREBPs) to control the genes governing the LDL receptor and the enzymes of cholesterol synthesis (14). In the first 10 yr of this effort, we qualified for POR by the handshake test. In recent years we have regretfully given up direct patient contact for the reasons outlined above. As a result, we have moved solidly into DOR.

Like ourselves, many M.D. scientists are working in DOR rather than POR. Table I lists some contemporary examples. Although their research does not involve patients directly, their discoveries have implications that are rapidly being translated by other investigators into the clinic.

POR. The father of modern POR is Archibald Garrod (1857–1936), who established the first metabolic ward devoted to clinical research in England. Stimulated by the black urine of a patient with alcaptonuria, Garrod advanced the concept of the inborn error of metabolism (15). In collaboration with a basic scientist, William Bateson, he further suggested that inborn errors are caused by genetic defects in enzymes that catalyze steps in biochemical pathways. His conclusion in 1908 that genes encode enzymes prefigured by 35 yr the Nobel prize-winning rediscovery of the same phenomenon in *Neurospora* by Beadle and Tatum, two basic scientists. Garrod remained a physician throughout his life, and he was eventually appointed Regius Professor of Medicine at Oxford.

Garrod's type of POR is still being performed, often with stunning success. Table II lists a few contemporary examples. Two of these involve the delineation of new syndromes: Lyme

Table II. Some Individuals Who Perform POR

Physician-Scientist	Clinical specialty	Discovery
Allen Steere and Steve Malawista	Rheumatology	Lyme disease
Michael Gottlieb	Allergy/Immunology	AIDS
William Waddell and Richard Loughry	Surgery	NSAID and colon cancer
Marcus Raichle; Antonio Damasio	Neurology	Visualizing and mapping the mind
Michael Thorner	Endocrinology	GH releasing factor
Mary Claire King (Ph.D.)	Genetics	Breast cancer gene
Barry Marshall	Gastroenterology	<i>Helicobacter</i> as cause of ulcers

disease by Steere and Malawista (16) and AIDS by Gottlieb (17). Syndrome delineation is a particularly precious branch of POR because it requires an intimate knowledge of disease. To recognize a syndrome as new, one must have a complete knowledge of all of the known syndromes. Piecing together evidence of a new syndrome is especially difficult because the facts are jumbled at first, and the syndrome only becomes clear when a consistent pattern is observed in multiple patients.

Another type of pioneering POR was performed by two surgeons, Waddell and Loughry, who first made the connection between nonsteroidal antiinflammatory drugs (NSAIDs) and colon cancer (Table II). Astutely, they observed the disappearance of rectal polyps in a patient with a form of familial adenomatous polyposis known as Gardner's syndrome (18) and correctly attributed this disappearance to treatment with sulindac, an NSAID that was given for unrelated reasons. This observation has since been confirmed in numerous clinical trials (19), and most recently its mechanistic implication—namely, that NSAIDs promote regression of colon polyps by inhibiting prostaglandin synthesis—has been supported by genetic studies in mice (20).

Marcus Raichle (21) and Antonio Damasio (22) are neurologists who pioneered the use of functional imaging techniques such as position-emission tomography (PET) and magnetic resonance imaging (MRI), combined with computers, to peer inside the minds of living human beings. These techniques now make it possible to visualize the neuroanatomical correlates of normal emotions (such as anxiety) as well as altered cognitive processes in stroke patients (such as aprosopagnosia or the inability to recognize faces). This frontier area in neuroscience is begging for creative patient-oriented researchers.

Michael Thorner is an endocrinologist whose careful clinical observations in a woman with Turner's syndrome led to the characterization of growth hormone-releasing factor (GHRF) as a molecular entity (23). The patient presented with classic acromegaly and an enlarged pituitary fossa, but the pituitary was hyperplastic, and not adenomatous, suggesting stimulation from another source. Thorner discovered that the patient had a pancreatic tumor that was stimulating the pituitary. The pancreatic tumor was removed, its GHRF activity was purified and sequenced (in collaboration with Wylie Vale, a basic scientist), and its cDNA and gene were cloned.

Mary Claire King is the only non-M.D. among those listed in Table II who is conducting POR. A Ph.D. geneticist, King identified the chromosome 17q21 breast/ovarian cancer gene (*BRCA1*) through classic linkage studies involving many families—a *tour de force* of genetic epidemiology that succeeded

only because King selected certain flagrantly affected families in which multiple young women had breast cancer, ovarian cancer, or both (24). She purposely ignored other families in which the inheritance pattern was not clear. Her strategy worked because she broke all the rules of epidemiology!

Barry Marshall, recipient of the 1995 Albert Lasker Clinical Medical Research Award, theorized that infection of the stomach with *Helicobacter pylori* caused duodenal and gastric ulcers. He went on almost single-handedly to demonstrate its validity in clinical studies involving epidemiology, bacteriology, and therapeutic trials with bismuth/antibiotic combinations (25). Although his work initially met with great skepticism, his persistence was rewarded, and today nearly all patients with peptic ulcers are cured by a combination of antibiotics and inhibitors of acid secretion.

The individuals described above, and others who perform successful POR, generally share four Ps: **P**assion, **P**atients, **P**atience, and **P**overty (Fig. 4). They all display a passionate curiosity about disease; they are deeply involved with patients; they have infinite patience; and they all withstand poverty in terms of grants. None of those listed in Table II was supported by a noncategorical private funding agency such as the Howard Hughes Medical Research Institute (HHMI). All struggled to obtain NIH grants. They all developed original ideas as a result of deep experience and commitment to patients, which allowed them to see patterns where no one else had seen them before.

Unfortunately, the creative type of POR that is highlighted in Table II represents the exception, rather than the rule. Too often physician-scientists do POR by following a fad and applying it to large groups of patients without deep clinical insight.

An example of this comes from our own field of lipoprotein research. In 1986, a group of investigators described a polymorphic restriction-endonuclease site in the gene encoding apolipoprotein A-I, a component of plasma high density lipoproteins, that appeared to be associated with a higher risk for

The 4 P's of POR

Passion
Patients
Patience
Poverty

Figure 4.

heart attacks (26). This opened the floodgates. Over the next 10 yr, more than 500 papers reported an association between either heart attacks or hyperlipidemia and a common polymorphism in one of eight different lipoprotein-related genes. To date, none of these associations has been robust, none has proved to be diagnostically useful, and none of them has provided new insights into the pathogenesis of hyperlipidemia or atherosclerosis. Ironically, the one apoprotein polymorphism that has proved important clinically has nothing to do with heart attacks. It concerns the role of the E-4 variant of apo E in predisposing to certain types of Alzheimer's disease. This major discovery by Strittmatter and Roses emerged from an independent approach to POR that did not follow a bandwagon (27). Their research differs from the apoprotein/heart attack association studies because they studied individuals from families with multiple relatives affected with Alzheimer's disease. By selecting individuals who were likely to have a strong genetic component, they made it much easier to demonstrate a significant association. The lesson is that it's okay to look for a needle in a haystack—but you better pick the right haystack!

The difficulty in identifying scientists who excel at POR is exemplified by the grantee list of the HHMI, which spends approximately \$300 million per year in support of medical research at 62 institutions across the United States. Of the 272 investigators currently supported by HHMI, 68% are Ph.D.'s and 32% are M.D.'s. One-half of the M.D.'s have a combined M.D./Ph.D. degree (28). Of the 272 investigators, 62% are doing basic research, 35% are doing DOR, and only 3% are doing POR. Indeed, HHMI supports the research of four of the eight M.D.'s in Table I who do DOR (Kan, Lefkowitz, Orkin, and Vogelstein).

The allure of basic research and DOR is also reflected in the list of young M.D.'s and M.D./Ph.D.'s who have received the prestigious HHMI Postdoctoral Fellowship for Physicians. Recipients of this award must have completed at least 2 yr of housestaff training after graduation from medical school. Despite their clinical background, only 3% of the 77 recipients in 1995 and 1996 chose POR; the vast majority selected either DOR (40%) or basic research (57%). The shortage of patient-oriented researchers supported by HHMI has persisted despite an active attempt by the leaders of the Institute to identify worthy recipients. HHMI's Medical Advisory Board has sponsored several conferences highlighting POR, and it has stressed POR in its invitations to medical schools to nominate new candidates for HHMI funding. People doing creative POR are hard to identify at an early stage before the implications of their insights have become well established.

One route to successful POR: collaboration

For all of the reasons described above, it is increasingly difficult for a single individual simultaneously to fill the roles of physician and scientist. There is one sure way to cover this spectrum: collaboration. The collaboration that we envision is not the large-scale multidisciplinary collaboration that is encouraged by NIH program projects or center grants. These have other worthy purposes. Rather, we are referring to an intimate collaboration between two individuals that allows them jointly to cover a range that neither could cover alone. The two collaborators might both have broad training in medicine and science. In this case the collaboration literally allows them to be in two places at one time—one in the clinic and the other in

the laboratory. They can exchange these roles periodically so that both can maintain both sets of skills. This is the type of collaboration that we experienced.

Perhaps more powerful is a collaboration in which one partner permanently plays the role of physician and the other is the scientist. Such collaborations work best when each of the partners has some training and experience in the discipline of the other so that they can readily exchange ideas and insights. Both partners may have M.D. degrees, or one may have a Ph.D. It is crucial that they interact as equals, each contributing the ideas that come from their own discipline. Partnerships based on subservience are doomed to failure.

Collaborations between physicians and scientists have generated many of the revolutionary advances in medicine. We have already referred to Garrod, the physician, and Bateson, the geneticist, who collaborated to delineate the genetic basis of inborn errors of metabolism. Another classic pair, less well known, is the team that discovered the antiinflammatory properties of cortisone (29–32).

The story of cortisone goes back to the 1930s and involves two pioneers, one a clinician, Philip Hench (1896–1965), and the other a Ph.D. chemist Edward Kendall (1886–1972). In 1929 Hench, a rheumatologist at the Mayo Clinic, noted that several of his patients with painful rheumatoid arthritis experienced dramatic improvement under one of two circumstances: pregnancy or jaundice (30). Hench theorized that these conditions induce the body to produce an antiinflammatory hormone that he called “anti-rheumatic substance X.” He carried out several trials involving oral administration of bile and intravenous administration of bilirubin or blood from pregnant or jaundiced donors, but none of these reproduced the ameliorating effect. He concluded that the only common biochemical denominator in jaundice and pregnancy was an elevated blood cholesterol level and that the adrenal gland, a rich source of cholesterol, might be the source of the putative “substance X.” To test this idea, Hench treated a few rheumatoid patients with a lipid extract of bovine adrenal glands, but no improvement resulted.

In the mid 1930s, Hench began to collaborate with Kendall, a chemist at the Mayo Clinic, who had earlier isolated thyroxine from thyroid glands and who was now attempting to isolate the substances from the adrenal cortex that maintain the life of adrenalectomized dogs (now known to be the steroids aldosterone and cortisol) (30–32). In 1934, Kendall isolated a crystalline material, called cortin, that consisted of 28 different steroids, 6 of which showed varying degrees of activity in his dog bioassay. These he named Compounds A to F. Hench administered the cortin mixture to his rheumatoid arthritis patients, but again no improvement occurred. He attributed the failure to the fact that cortin was a complex mixture. Undeterred, he determined to treat patients with single pure adrenal steroids.

Separating closely related steroids was a difficult problem that required 10 yr and 150 tons of beef adrenal glands. Eventually, Kendall separated the six active steroids, delineated their structures, and learned how to synthesize them on a small scale (32).

The first steroid to be purified, Compound A (11-dehydrocorticosterone), proved ineffective in Hench's patients, but Hench remained optimistic. By 1946, Kendall had isolated Compound E (cortisone). Although it had only weak activity in the adrenalectomized dog assay, Hench was convinced that cortisone was his long-sought “substance X.” However, Ken-

dall was unable to synthesize sufficient quantities to administer to patients.

Hench's dream finally came true, thanks to a collaboration that Kendall arranged with Merck and Co., Inc. Under the direction of Lewis H. Sarett, Merck chemists devised a 37-step chemical synthesis for cortisone. This was the most complex synthesis that had ever been conducted in any drug company. In 1948, the Merck scientists were able to produce several grams of cortisone, just enough to treat *one* rheumatoid patient with 100 mg intramuscularly for 9 d. This time, dramatic improvement occurred: swelling and tenderness abated, and the immobilized patient rose from bed and walked the halls of the Mayo Clinic.

Hench and Kendall presented their work publicly at the 1949 annual meeting of the AAP, where it received an unprecedented standing ovation (31). After the presentation, Walter Bauer, Chief of Medicine at the Massachusetts General Hospital and one of the world's most respected clinicians, rose and remarked, "I can truthfully say that I have never seen anything so dramatic in all my years of seeing patients" (33). The Karolinska Institute agreed. The next year Hench and Kendall (together with Tadeus Reichstein who discovered the mineralocorticoid 11-deoxycorticosterone) received the Nobel Prize in Physiology or Medicine.

Cortisone could not have been realized without collaboration between a passionate and committed clinician, a basic scientist, and a pharmaceutical company. The key to the whole process was a physician who had sufficient confidence in his clinical acumen to sustain his work despite numerous failures. Flowers and Melmon have called such individuals "clinical champions," and they have pointed out many other instances in which therapeutic breakthroughs were inspired by such committed physicians (34).

Successful collaboration on the stages of Broadway and Stockholm

Intimate collaborations are not only successful in science; they also work on Broadway. Partnerships created most of the classic Broadway musicals, which may be the most original cultural contribution of America in the twentieth century. In such a partnership, one person creates the music (analogous to Hench), the other writes the lyrics (Kendall), and both collaborate with directors and choreographers (Merck) to produce an integrated masterpiece (cortisone as a useful drug).

One of the legendary partnerships of Broadway paired the composer Richard Rodgers (1902–79) and the lyricist Lorenz Hart (1895–1943). Their most famous product, *Pal Joey*, is considered by many to be the first modern Broadway musical (35). It was the first time that music, songs, and dancing were integrated to advance a sophisticated plot.

Pal Joey initiated the Golden Age of Broadway (35), setting the style for later classics like *Oklahoma*, *South Pacific*, *The Sound of Music*, and *My Fair Lady*. Its most famous song epitomizes the confused state of the modern clinical investigator: "Bewitched, Bothered, and Bewildered"—*bewitched* by the thrill of science and clinical medicine, *bothered* by the need to choose one or the other, and *bewildered* because he or she can't decide between the two.

If ever there were a committed collaborator, it was Richard Rodgers who worked 42 yr with two lyricists: Hart (1919–41) and Oscar Hammerstein II (1941–60). According to Rodgers, in order for a partnership to succeed the two partners must

Table III. Nobel Prize-winning Partnerships in Biomedical Science

Partners	Years	Dates
Cori and Cori	35	1922–57
Stein and Moore	33	1939–72
Cournand and Richards	30	1932–62
Brown and Goldstein	25	1972–present
Hitchings and Elion	23	1944–67
Berson and Yalow	22	1950–72
Hubel and Wiesel	20	1958–78
Bishop and Varmus	19	1971–90
Hench and Kendall	16	1934–50
Jacob and Monod	9	1957–66
Watson and Crick	2	1951–53

like each other, must be able to spend long periods of time without getting on each other's nerves, and must be willing to argue and fuss about all of the details, but not about the general strategy or the overall goals. The composer of the music must be able to say "that song stinks," and the lyricist must be able to say "that music stinks" (36).

Partnerships in science are not as common as they are on Broadway, but they occur, and when they do they are likely to achieve success. Table III lists 11 partnerships in medical science that led to recognition on a stage—not on Broadway but in the Concert Hall in Stockholm. From our own partnership of 25 yr, we can state that the most creative ideas emerge from a constant dialogue that allows us to think aloud and to get rid of false notions rapidly so that the good ones can emerge. Being able to say to each other "that idea stinks" stops the nonsense and allows the fun to begin. Moreover, when an experiment works, you don't have to explain its significance to anyone. You have an understanding partner who shares the thrill of that moment.

POR: salvation for the biotechnology industry

The biotechnology industry offers our best hope for the discovery of radical therapies for the most resistant diseases, but the development of approved products has been painfully slow. The rate-limiting factor is not the imagination of the basic scientists, nor is it their ability to isolate genes, to produce recombinant proteins, or to screen for small molecule agonists or antagonists. Nor is there any shortage of clinicians who are willing to test the therapies that emerge from the industry. Indeed, academic medical centers are eager to test new treatments, if only to distinguish themselves from competing non-academic hospitals. Rather, the rate-limiting factor is the clinical scholar with the analytical insight to point the biotechnology companies toward the Achilles heel of a stubborn disease. There are simply not enough Philip Hensch or Barry Marshalls. As a result, the industry proceeds in a hit-or-miss fashion with the vast majority of tested therapies failing.

The difficulties faced by the biotechnology industry are reflected in the statistics. At the end of 1996, the biotechnology industry consisted of 1,287 companies, of which 294 are publicly owned. It employs 118,000 people, about one-third of whom are Ph.D. scientists and virtually none are patient-oriented researchers. The industry had a market capitalization of

Table IV. Biotechnology's Successes: 17 Drugs Approved by FDA

1982-Insulin	1991-G-CSF
1985-Growth hormone	GM-CSF
1986- α -interferon	Glucocerebrosidase
Anti-OKT3	1991-IL-2
Hepatitis B vaccine	Factor VIII
1987-tPA	1993-DNAse
1989-Erythropoietin	β -Interferon
1990- γ -Interferon	1994-Anti-IIb/IIIa
	1997-Factor IX

\$83 billion, product sales of \$11 billion, research and development expenses of \$8 billion, and an overall net loss of \$4.5 billion (37). In other words, the entire biotechnology industry is about the size of Merck & Co.—without the profits!

To date, the biotechnology industry has developed 17 re-

The Biotechnology Industry in 1997: From the Surreal to the Real

1 New Gene per Day
1 New Company per Week
1 New Drug per Year

Figure 5.

combinant drugs or vaccines that have been approved by the FDA (Table IV). Some of these drugs are major contributions to therapeutic medicine, and in this sense the biotechnology industry is a success. On the other hand, the expense and waste in producing these drugs is enormous, as revealed in Fig. 5. On average one new gene is cloned and characterized each day, one new biotechnology company is formed each week, but only one new recombinant drug is approved by the FDA each year. As many as 700 therapeutic products are currently



CGGAAAGGA	AGCAGGTCT	CTGAAGAAAT	ACTTCAGGAG	TAGAAAGAGG	AAGCTAGAGG
GAGTTAGTAT	ATGTCCTAGAG	GTGTAGTAAA	CTAAAACAAG	TCTTGAATTG	CATACCGCCA
AGGGAAACTG	CAACGCCTGT	ATTACTAGAT	AGCTTTCATC	AACAGCTCAA	AACCGACAGA
AATTTGGTTT	GGATCCCATG	CCCATGACCC	TGCCAGCTGA	CAATTCCTAAG	CATGCGCAA
TGGCCCTTTA	TGTGAAGTAC	CTGGTTTTTC	CATTTCTGT	TTTACCATAG	GCCTCAGTTC
TCATTCTATT	AGATTA AAAA	AAAAGAATAC	AATGGAAGCC	AAGTGATTAA	GCCTTCCTTA
AACCGTATTA	ACCTACAGAA	AATGTCCAGG	GAAATGGTCT	ATTTCTTATT	CTATTTTTGA
TCTCCATCCA	CTTCCCTCAG	CTTTGGCCTG	AAGCTATCTT	TAAAGGTACC	CTGTACAAGC
TGTTTCGATA	GGACACATCT	CAGTGGCAGA	TAAATGCAA	AGTTATATA	TGTATGAACC
GTCTTAAGAC	TATAGTAATA	TCTTCACTTG	AAAAGCCCT	CTATTATTCC	TATCTCAGAT
TAATCGCACC	TGGCTCTACA	AAGCTAGTCT	GGACAGACAT	TTAAACAATT	ATCCTCTAAG
AAAAACCAA	GTGAGCATCC	CATCTGTTCC	CAGTCAAATG	ACCTAGAGCA	AAGGACTAGG
CAATGAATT	TGCTTTGTAT	ATGAGTGAGA	GCAAACACTC	TTTATGTAC	AACCTGGGTG
AACGGTTACG	TTGGAGTTAA	AGGTTAGGAA	GAAAACCAA	GGGTAAGAGC	TGTTGTTCTG
TGTATATTTT	GTAGAAGCAT	GTGTGTTGTT	GGTTTTTGTG	TATGTGTGAG	TCTGAAAGAG
TTGACAGATT	ATAACTCAGA	TGCTTACTC	AGAGCATATG	CCTTCCATT	TTCCCATTA
GCAGACATCT	CATACCCCAA	ATAGCTAATA	TTTTGATAGC	TATGATCCTG	AACGGCCAAA
TATATTTTAG	GCCTTTTCCCT	TGGCAAGGAT	GTTTGGTCAG	GGGTTGGCAA	AAATAATGCT
CACCAGAAAG	TAGTAGAACG	CTCCAGGAAG	CAAGTCTTTG	TCAGGAGTCA	GACTAGCTAC
CTGGCCTAA	CTAGCCTACT	GAGCTGAGAG	ATGTCCAATT	TCCCCCAAT	ACACTAACCA
TTCCAATTGC	TTAAACAAAT	ATGTTCAAGT	GTAACATCA	ATACCAGTAT	ATAACAGTGT
AGCCAGACAC	ATGGTCTTAT	GACCGCGTA	CTTACGCAGG	GCTTTGCACT	GAGACAGGTC

Ceci n'est pas un médicament.

Figure 6. Top: *La trahison des images* (The Betrayal of Images). René Magritte, 1929.

Text reads "This is not a pipe." Bottom: A contemporary version of Magritte's painting adapted to the biotechnology industry. Text reads "This is not a drug." © 1997 C. Herscovici, Brussels/Artists Rights Society (ARS), New York.

undergoing clinical trials by 167 companies (37). But 14 of the last 16 drugs failed in Phase 2/3 studies.

If Magritte, the surrealist, were alive today, he might represent the situation as shown in Fig. 6. The top panel shows a reproduction of Magritte's famous painting *The Betrayal of Images* in which he reminds us that the image of the pipe is not the same as the pipe itself (*Ceci n'est pas une pipe.*). The bottom panel shows a modern version that reminds us that a gene sequence is not a drug (*Ceci n'est pas un médicament.*).

Role of the M.D./Ph.D. in biomedical research

If being a physician-scientist is so difficult, how can we justify the NIH-supported program to train students to become both M.D.'s and Ph.D.'s? Far from being superfluous, we believe that M.D./Ph.D. programs are central to the future of research medicine. Our belief is so strong that we both serve on the steering committee for this program at our school and one of us (M.S. Brown) has become the director of the program.

Although the path to an M.D./Ph.D. degree is tortuous, certain individuals can navigate it because, like Shannon's career, it is compartmentalized in time and place. During the years of clinical training, M.D./Ph.D. students are not differentiated from their purely clinical counterparts. They master clinical skills and develop the same compassion and commitment as do all medical students. In the ideal case, they complete their clinical training and become capable, confident physicians. During their research years the students are not differentiated from other graduate students. They have the same intimate exposure to a research mentor, and they learn not merely the techniques but more importantly the thought patterns of basic scientists.

When all of this training is finished, the M.D./Ph.D. can choose from the entire spectrum of research, from basic science to DOR to POR. The choice need not be irrevocable. Like many of the individuals in Table II, M.D./Ph.D.'s may start by identifying a patient-related problem that is ripe for attack. At this stage they are doing POR. Later they can take their problems deeper to DOR and even to basic research. During this evolution, the M.D./Ph.D. may have to abandon the role of physician, but the medical training can hardly be considered wasted. This training provided the inspiration that started the whole process. The M.D./Ph.D. may also choose to collaborate with another scientist who shares the same goals, thereby making it possible to continue clinical and research work for a longer period. The fundamental point is that whatever place in the research spectrum is chosen, the M.D./Ph.D. will benefit from prior exposure to the entire spectrum.

Summary and recommendations

This article is specifically directed toward the physician-scientist. We have not mentioned the enormous contributions of Ph.D.-trained basic scientists, nor have we discussed their growing contribution to DOR. Basic scientists need no special recognition; they are moving ahead rapidly. In contrast, patient-oriented scientists are currently experiencing an identity crisis, and they need special attention if they are to survive. Patient-oriented researchers may be *bewitched, bothered, and bewildered*, but they are still *beloved*. To take full advantage of the opportunities created by basic research, DOR, and the biotechnology industry, we need a larger number of thoughtful, dedicated clinical scholars who care for individual patients and who have the time and resources to achieve a deeper under-

standing of normal and deranged function at the level of whole human beings.

We propose the following recommendations:

1. *Reinvigorate the intellectual core of academic medicine.* This can be accomplished by training and supporting scholarly physicians who are broadly versed, intensely curious, and infectious in their ability to stimulate others to think deeply about human disease. A prototype is Victor McKusick, the physician who meticulously classified the heritable connective tissue diseases (38). This work, accomplished in the 1950s and 1960s, provided the framework that allowed disease-oriented researchers to discover the molecular defects three decades later. A modern-day McKusick might identify new syndromes by applying the wealth of new genome information or by taking advantage of the recent identification of new hormones (leptin and thrombopoietin), cytokines (IL-10 and IL-15), and angiogenesis factors (VEGF and angiopoietin). Obesity, non-insulin-dependent diabetes mellitus, inflammatory bowel disease, autoimmune diseases, and metastatic cancer seem ripe for such an attack. The uniqueness of the clinical scholar's approach lies in astute observation of individual patients. Endowed professorships should provide full salaries for POR scholars so as to free them from the service burden of caring for large numbers of patients. The endowed scholar should select patients on the basis of academic interest and not because of community need.

The NIH could supplement this effort by providing a small number of career development awards targeted to clinical scholars. We stress that these awards should differ from center-type awards that go to individuals who head large multidisciplinary clinical efforts. These are already well supported. Instead, we are talking about individual clinicians who see patients daily and derive their inspiration from direct patient contact. Such an individual rarely, if ever, has the time to head a large multidisciplinary center.

2. *Modify the academic reward system so that it encourages collaborations.* We chose the Broadway model because it carries an important message about credit. When we enjoy a Broadway show, we care not that the music was written by one person and the lyrics by another. We simply enjoy the product. Yet, somehow, we believe that a scientist can achieve greatness only if he or she produces a body of work in an independent fashion. University promotions committees stress independence as an essential criterion. The front sheet of all NIH grant applications has space for only a single Principal Investigator, even though many may work on the project. The academic community should recognize the power of partnership and reward it.

3. *Support the bridge builders.* In view of the increasing need for cooperation between clinicians and scientists, it is most important to produce individuals with training in both areas who can build the bridges that allow the two disciplines to interact. Many approaches should be used. In addition to M.D./Ph.D. programs, we must enlarge predoctoral programs that immerse medical students fully into research, if only for a year or two. One prototype is the HHMI-sponsored program that allows medical students to spend 1–2 yr doing laboratory research at NIH or any U.S. medical school. M.D.'s can also be introduced to research at the postdoctoral level. One program is the Physician-Scientist Award of NIH, which provides scientific fellowships for physicians who have completed clinical training. Finally, clinical topics should be introduced into the

curriculum of Ph.D. graduate programs in biology, and the graduates should be encouraged to work on problems with clinical impact. Each of these approaches has different virtues and drawbacks. It is crucial to provide diverse options, so as to offer a wide choice to individuals with different interests and talents.

4. *Encourage innovation.* As in all types of research, in POR the most precious qualities are originality and creativity. Many would argue that these qualities are inborn and cannot be created. Even if this is true, we must provide the environment that permits those with inborn talents to learn and practice their art.

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