Future Directions

Now that the human genome has been largely sequenced, one can expect that the most common polymorphisms will be identified over the next several years. Given the momentum of ongoing research, we will determine how these genetic variants are related to risks of important human diseases. However, to do so without interminable inconsistency in results will require carefully designed studies and probably the pooling of results unaffected by publication bias to obtain the best overall estimate of associations. These results will no doubt lead to better increase understanding of the pathogenesis of human disease and to the development of new pharmacologic agents and more individualized interventions. These benefits are likely to be greatest for treatment rather than prevention because in treatments a single disease and biological pathway is targeted and adverse effects of powerful agents are appropriately more acceptable. Recognizing that more effective treatments are desirable, our resources allocated to treatment already massively outweigh those spent for disease prevention, and even preventive strategies are heavily biased toward pharmacology rather than supporting improvements in diet and life-style that could be more cost-effective (*21*). For example, treatment of serum cholesterol with statins (*22*) alone could cost approximately 30 billion dollars per year in the United States and will have only a modest impact on coronary heart disease incidence (*23*). The inherent problem is that most pharmacologic strategies do not address the underlying causes of ill health in Western countries (Fig. 1), which are not drug deficiencies. (An effective pharmacologic treatment of obesity may be an exception because the adverse health consequences are so numerous and the condition of being overweight has become the norm.) The use of research approaches that integrate environmental factors including diet and other life-style variables with genetic information has the potential to clarify the roles of both environment and genotype in disease causation. This balanced approach should provide the best data to make informed choices about the most effective means to enhance health.

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23. The overall effect of using statins for primary prevention on rates of coronary heart disease in the U.S. population (*22*) may be modest because treatment reduces risk by about one-third in those receiving the drug and a substantial proportion of cases will occur among untreated persons. For example, on the basis of data from the MRFIT study (*24*), 35% of coronary heart disease occurred among the 20% of men in the population with the highest serum cholesterol; if this is reduced by one-third, the total population rate is reduced by 35% x 0.33 = 12%. The annual cost of treating 20% of U.S. adults over the age of 40 is roughly $1400 per person per year (*21*), multiplied by 24 million persons equals ~$34 billion annually. Prosser *et al.* have documented that widespread use of statins for primary prevention is not cost-effective at present prices with the use of widely accepted criteria (*21*). Use among patients with existing coronary disease or diabetes is better justified.
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VIEWPOINT

Complex Disease and the New Clinical Sciences

Jonathan Rees

Medical research today is dominated by a genocentric point of view. At the same time, clinical discovery and patient-oriented research have become less common. Here, I suggest that these developments are interdependent, each representing the flip side of an inaccurate view of how clinical advance occurs.

The last 25 years has seen medical research dominated by a genocentric view of discovery. The icon of the biological sciences, if not of everyday life, has been DNA. Today, even sunblock manufacturers feature images of the double helix on their advertising material. We have, we are told, entered a new golden-period of medical discovery. Medical research funding and personnel have grown as never before; it is implied that, now that we have solved the easy problems (that is, identified genes that cause a myriad of Mendelian disorders), we need new postgenomic approaches to solve "complex disease" and move from "bench to clinic." No longer are we to be satisfied with discovering the causes of rare diseases, but we must now set in place new strategic structures to study the big three: cancer, psychiatric disorders, and cardiovascular disease. For this, it is said, we need human-genome-project-like science, sequencing of a range of model organisms, and a host of "omic" projects—proteomics, metabolomics, etc. A giant cataloging of molecular natural history is entertained, a move from the small to the large scale, all to solve disease.

At the same time, an alternative set of views is being given more credence(*1–3*). Despite the mushrooming of basic research, clinical breakthroughs have become less common. The therapeutic revolution that transformed medicine in the 1950s and 1960s has petered out. New drugs to market are fewer than ever, the range of diseases of interest to the major pharma diminishing, and the success rate of either pharma or biotech is low (*4*). Clinical discovery and patient-orientated research are also noteworthy, because of their relative absence

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(*1*, *5*, *6*). Even when mentioned, their role is misunderstood as the mere translation of real discoveries made at the bench into the health care system or—more worryingly—confused with outcomes research (*7*, *8*), an activity sometimes (and incorrectly) seen as a mere checklist scoring of how well patients feel after an intervention.

The loss of confidence in clinical science is signaled by the curious renaming of once proud areas of academic endeavor. Neurologists are now clinical neuroscientists, and departments of pharmacology are now departments of pharmacological sciences. My physician colleagues will, only under duress, admit they are academic dermatologists; they prefer molecular dermatologists, medical cell biologists, or skin immunologists. It is as though kudos can only come from the latter. The American polymath and Nobel laureate Herbert Simon, drawing parallels with what had happened with engineering schools, presciently observed this phenomenon over 10 years ago (*9*). He pointed out that medical schools had become schools of molecular biology and biochemistry, rather than schools of medicine, an insight to which I shall return.

Here, I wish to draw these two themes together and show that a common set of misunderstandings underlies, on the one hand, much hyperbole surrounding the role of genomics in disease prevention and therapy and, on the other, the crisis in clinical research. I suggest that these problems are interdependent, each representing the flip side of an inaccurate view of how clinical advance occurs. Medicine is not synonymous with biology (*10*), and contrary to what many would think, as Paul Janssen has pointed out, the gap between the clinician and the basic scientist has increased, not diminished, in the last quarter century (*11*). It is this gap that needs to be closed but, unlike many, I don't believe it will be resolved by clinicians learning more genetics; rather it is the geneticists and biochemists who need to learn some medicine.

Complexity and Simplicity

The elucidation of the molecular basis of heredity by Watson and Crick and others, and a sequence of revolutionary technical advances in the ability to manipulate nucleic acids, meant that for the first time experimental genetics was no longer confined to model organisms, but could be used to elucidate the basis of human disease.

Research in most medical specialities was transformed, none more so than dermatology. The availability of genetic tools allowed improved disease classification, fresh mechanistic insight, and a chance to correct many of the half-truths that passed for authoritative clinical opinion. Textbooks could now be rewritten. Interest in what were once just rare and neglected diseases flourished, and the availability of more precise information about modes of inheritance brought major advance for the unlucky individuals who suffered from some of the rare but devastating genetic skin diseases. Real advances were made.

Recognition of these changes was perhaps passed over too quickly in the rush to map out the new challenge: the genetic bases of "complex disease." Yet, it was clear at the time, and has become ever more so, that this mantra rested on some fundamental misconceptions (*12*, *13*). Complexity may, as an operational criterion, be useful to a geneticist to describe a lack of simple correspondence between genotype and phenotype but, from the point of view of clinical medicine, it is simply the inverse of therapeutic insight. It says more about the state of our knowledge than about disease.

Just as it is obviously facile to argue that because a disease is genetic, therapy needs to invoke genetics, it is a mistake to imagine that complex disease may not be solved by simple approaches or that their causes are not simple. The grave danger of terms such as "multifactorial" or "complex" is that they may justify the belief that solutions will come only from large and expensive managed projects rather than from simpler approaches.

Pernicious anemia is as complex a disease as one could imagine. It involves autoimmunity and complex inheritance, and it affects almost every organ system. Yet, once mechanistic insight was obtained, treatment was simple: injection of the missing vitamin, B_{12}. Successful therapy relied not on reversing the cause, because cause in this sense can be operationally defined in all sort of ways, but on finding the Achilles' heel of the condition that allowed therapeutic intervention. Similarly, syphilis, as has often been remarked, remains treatable because the microbiologists got there before the immunologists could "explain" the disease. The cause of disease is therefore not some objective God's eye summary of pathophysiology, but rather an operational statement of where we think the Achilles' heel of a disease might be.

Susceptibility to tuberculosis has a large inherited component, a fact confirmed by recent work but suspected before the infectious agent had been identified (*14*). Yet, this notion of cause was of little use to the successful paradigm that led to identification of a causative bacillus, vaccination, and chemotherapy. If anything, it would have been distracting. Diseases don't exist in their own right but as alterations in complex systems of homeostasis. Medicine, it seems, has little regard for a complete description of how a myriad of pathways result in any clinicalstate. Rather, its goal remains pragmatic; it defines cause by how successful intervention might be obtained, how one, of many rate-limiting pathways, may be circumvented. Medicine is more engineering than grand theory.

Rothman has pointed out that all diseases are 100% genetic and 100% environmental, and yet it still remains common for authors seeking to bolster genetic approaches to disease to misuse heritability as though it referred to the proportion of disease caused by genetic factors (*15*). Heritability is not about cause per se, but about the cause of variation of a trait in a population; the two are not the same. That psoriasis has high heritability in a particular population is a statement about variation, not about the proportion of a disease caused by genetic factors, let alone therapeutic insight (*16*).

Which Way: Bench to Clinic, or Clinic to Bench?

Critics would say that I am missing the point. That my discussion of technical definitions of terms such as heritability is, at best, peripheral. Although many have belatedly admitted that for the majority of complex disorders, prediction based on genetic analyses may be less helpful than once thought (*12*), they maintain that the explosion of knowledge in basic biology will transform medicine and

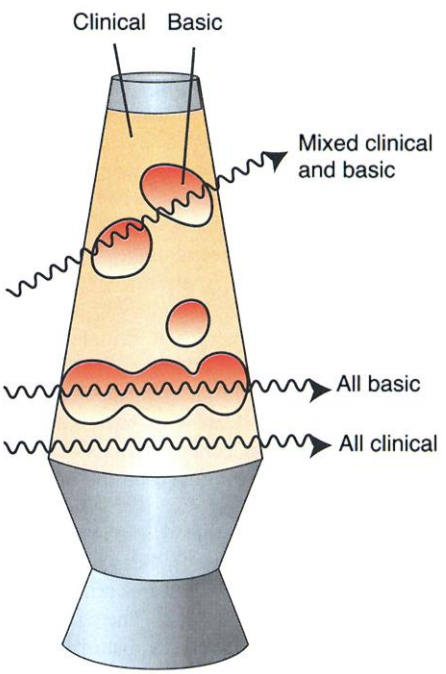

Fig. 1. The lava lamp model of clinical advance. Clinical advance is represented by traversing the lamp. the liquid and the more solid material, represent clinical and "basic" science, respectively. Advance can occur by several trajectories, and there is no one path to a useful solution. Some solutions will involve just clinical science, and others will involve a mixture of basic and clinical science. Importantly, what are defined as basic and clinical science, and their relative positions, may change with time. Rate limiting is the ability to see through the lamp and then traverse it.

drug discovery. This is a powerful argument that one would be foolish to ignore or even to try to rebut completely. I don't. My point is that this approach is necessary but not sufficient. The dated model of science, as a pyramid, with biochemistry and genetics at the base, leading to clinical advance at the apex, is wrong (*10*, *17*, *18*). It fails both as a description of clinical advance and, curiously, of how complicated biology is (Fig. 1).

Some Cameos of Clinical Discovery

The financial hegemony of the linear "basic to applied" paradigm does, however, account for some of the crisis in patient-oriented research and a degree of slowing in real therapeutic advance. This apparent heresy I need to justify, and to do so, I will use examples from the dermatological world; few diseases are more common.

Acne is almost ubiquitous in the teenage years and, in a minority of persons, it is the cause of significant scarring and subsequent emotional handicap. The pathophysiology centers around abnormal bacterial colonization and a causal correlation between sebum excretion and disease severity. It is genetically complex.

Until the 1970s the backbone of therapy relied on antibacterial approaches, but research programs focused on defining the endocrine determinants of sebum control, principally androgens. The rational research goal remained a topically active antiandrogen. All of this was overturned when systemic retinoids, administered for other reasons, were seen to abolish acne, particularly the severe cases (*19*). Once the therapeutic effect had been demonstrated, the inhibitory effects of retinoids on sebum excretion were discovered. And whereas a half century of previous work had documented the multitude of effects of retinoids on skin, none of the model systems had predicted the clinical role. Nor, in one of the hottest areas of basic science, has the elucidation of the various nuclear signaling pathways improved on the original drug (*17*).

Seborrhoeic dermatitis is a skin disorder affecting a few percent of the young adult population, and it shows features reminiscent of both psoriasis and eczema. The pathogenesis was thought to involve a disturbance in epidermal hyperproliferation centered around the follicle. In the early 1980s, in clear parallels with Marshall's work on *Helicobacter* and peptic ulcer (*20*), Shuster reviewed earlier (and ignored) work, seized the opportunities offered by a new family of effective antifungal drugs, and showed that the presence of a particular yeast was rate limiting for the presence of the disease: no yeast, no disease (*21*). He went from cause to successful treatment in 2 years.

Psoriasis affects about 2% of most Western populations, is genetically complex, and runs a fluctuating course without apparent explanation. Major histocompatibility complex associations and exacerbation of the disease after streptococcal sore throat suggest an important role for the immune system (or infection with an as yet unidentified infectious agent). Advances in therapy have revolutionized clinical care in the last 30 years and almost all have centered around clinical observation and insight from the clinic. Thus, when psoriatic patients reported that natural sunshine improved their disease, therapeutic ultraviolet lamps with a broad spectrum were tested and found to be effective, although their mechanism of action remained unclear. Nonetheless, even in the absence of a precise mechanism of action, experiments led van der Leun and colleagues to persuade Philips (the ultraviolet lamp manufacturers) of the need for new lamps with more specific and powerful spectral outputs (*22*). The result was a new generation of narrow band 311-nm phototherapy lamps that now provide the basis of outpatient treatment of psoriasis. Similarly, Fitzpatrick and colleagues, cognizant of work showing that topical photosensitizers such as psoralens had biological effects on skin, invented oral psoralen photochemotherapy (PUVA) for severe psoriasis (*23*). Again, approaches from clinicians to lamp companies were necessary.

Nonmelanoma skin cancer is the commonest human cancer. In the United States alone, more than 1 million people develop new basal cell carcinomas each year. That ultraviolet radiation (UVR) causes skin cancer was suspected over a century ago and was confirmed when dermatologists started using UVR lamps to treat skin disease (*24*). We now have a precise picture of the early stages and genetic determinants of skin cancer, and yet the current epidemic is being successfully managed by sun avoidance strategies, earlier clinical intervention, and step-by-step improvement in surgical therapy, all independent of advances in "basic" research (*24*).

What Characterizes Clinical Science?

Many, if not all of the above examples of clinical science share certain characteristics. First, that a disease is complex or multifactorial does not imply that simple solutions cannot be found or that clinical advance following insight cannot be swift. Second, although it is comforting to many, including funding agencies, to imagine that it is all mere serendipity, this is a travesty of reality. Most of the key insights described above came from clinical investigators with a history of success in more than one field. One advance may be luck; two advances suggest the presence of something special. Third, many of these clinically driven therapeutic advances are not marginal, but astonishingly effective. Acne is a chronic disease and yet a short course of retinoids reverses the disease, even when the drug is stopped. How many other chronic diseases can be so reversed? Psoralen and UVA (PUVA) therapy and outpatient treatment provided better results than the traditional inpatient stay of 1 month.

Finally, a precise formulation of pathophysiology was not always necessary to think rationally about therapy; indeed for some of the examples, the earlier models of therapeutic action were probably wrong. The corollary of this is that the ability to experiment or make observations at the level of the whole human is incredibly important. Our knowledge of biology is such that predictions from putative model systems to patients are frequently, if not usually, inadequate. The ability to take a disease to pieces in molecular terms is not the same as being able to plan interventions with the necessary precision, another example of Anderson's constructionist fallacy (*25*). Drugs with a multitude of effects ("dirty" drugs) like ultraviolet radiation are often more effective than rational ("designer" drugs).

Advancing Clinical Science

This essay will not have achieved its purpose if it appears dismissive of the need for basic biochemistry or genetics. Rather, my view is that such science complements but does not replace or specifically serve clinical science.

Nevertheless, there are real issues that need confronting and require a relative shift in resource from lab to clinic. The term basic is, in respect of medical discovery, all too often, misleading; basic is that which leads to solution, not a descriptor of size of the experimental unit of interest. Clinical science is therefore as basic to medicine as biochemistry. Clinical advance, of course, relies not just on advances in biology, but in chemistry and physics too. Listings of Nobel prize winners suggest that the medical importance of the latter is easily underestimated (*26*). Clinical science remains, to use Dyson's analogy, a craft science, like some software design, decentralized and always at the edge of academic disciplines (*27*). Medicine, as my quote from Herbert Simon suggested (*9*), has more in common, in terms of intellectual temperament, with engineering than with pure science.

We also need to focus clearly on and demarcate forcefully what we mean by clinical science. Goldstein and Brown define patient-oriented research as research in which the investigator still shakes hands with his or her subjects (*1*). There is much to commend this terminology as being more useful than the different activities that pass as clinical science.

Either way, we should be careful neither to conflate real clinical science with mere testing of technologies (such as drug trials) nor with outcomes research (*7*, *8*). We need all these activities, and there is room for real intellectual innovation in the way we carry them out. But clinical science remains distinct—namely, solving disease based on the experience of seeing, thinking about, and treating individual patients. How did we forget?

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VIEWPOINT

Maneuvering in the Complex Path from Genotype to Phenotype

Richard Strohman

Human disease phenotypes are controlled not only by genes but by lawful self-organizing networks that display system-wide dynamics. These networks range from metabolic pathways to signaling pathways that regulate hormone action. When perturbed, networks alter their output of matter and energy which, depending on the environmental context, can produce either a pathological or a normal phenotype. Study of the dynamics of these networks by approaches such as metabolic control analysis may provide new insights into the pathogenesis and treatment of complex diseases.

Cell and molecular biology, in conjunction with new theoretical developments, have, in the past decade, taken us from a grossly naïve view of genetic determinism (that complex traits are caused by a single gene) to the stark reality that almost all human diseases are complex context-dependent entities to which our genes make a necessary, but only partial, contribution (*1*). Molecular biologists have rediscovered the profound complexity of the genotype-phenotype relationship, but are unable to explain it: Something is missing. The missing element was described 35 years ago by Michael Polanyi, who characterized live mechanisms and information in DNA as "boundary conditions with a sequence of boundaries above them" (*2*).

Biologists today who work on systems biology refer to these boundary conditions as levels of constraints, or control constraints, outlined in Table 1. Molecular biology has shown that in the progression from genotype to phenotype, many levels of control are introduced. Each control level is defined by a dynamic system of self-organizing proteins, the output of which is governed by laws that are still poorly understood. Polanyi illustrated his concept of levels of control with a metaphor from the game of chess: "The strategy of the player imposes boundaries on the several moves which follow the laws of chess, but our interest [in experimental biology] lies in the boundaries, that is, in the strategy, not in the several moves as exemplifications of the laws." Molecular biology, in identifying control levels, has focused on the "moves" of genes and proteins but has largely ignored the strategy used by dynamic protein networks that generate phenotype from genotype. Systems biology is all about finding the strategy used by cells and at higher levels of organization (tissue, organ, and whole organism) to produce orderly adaptive behavior in the face of widely varying genetic and environmental conditions (*3*). At the center of this effort is a need to understand the formal relationship between genes and proteins as agents, and the dynamics of the complex systems of which they are composed. Much effort has been spent in attempts to predict phenotype, first from genomic, and then from proteomic, databases. But these databases do not contain sufficient information to specify the behavior of a complex system. The "systems" relationship between genotype and phenotype is perhaps best represented in the formulation by Howard Pattee (*4*).

Dynamics describes laws (operating rules) controlling the behavior (the phenotype) of any self-organizing system of gene-encoded proteins. Therefore, we expect that the various transitions shown in Table 1 will involve laws governing an orderly interaction between proteins; between proteins and environmental signals; and, in the case of DNA binding proteins (level 1, Table 1), between proteins and critical small molecules such as nicotinamide adenine dinucleotide (NAD)/NADH, where molecular concentrations are symbols of the entire bioenergetic state of the cell. DNA binding proteins that also sense levels of NAD/NADH are able to transmit that "sense" of energy readiness of a cell to information that changes the pattern of gene expression and, therefore, changes the energy-dependent cellular phenotype (*5*–*7*). The systems controlling transitions from transcriptome to proteome (level 2) and from proteome to complex systems (level 3) are presently foci of intense research activity, but we are still mostly ignorant of the laws governing the context dependency and integration of environmental signals into the output patterns of those systems.

In contrast, at the level of metabolic networks, it is clear that the phenotype (the output of energy and matter) is predictable from known laws of chemistry: laws of kinetics and thermodynamics (*8*). Metabolic

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