Computer-Assisted Drug Design. Part I. Conditions in the 1980s

James P. Snyder

Drug Design, Searle Research & Development, 4901 Searle Parkway, Skokie, Illinois 60077

I. INTRODUCTION

Every major pharmaceutical firm conducting research in the 1980s introduced computational chemistry into the discovery matrix. One of the interesting direct consequences of this investment is that the field of computational drug design has developed primarily in industry. Pioneering university-based quantum mechanical,[1–3] force-field,[4–7] and graphics-oriented[8] methods have been extended[9–11] and applied within multipronged approaches to complex questions of enzyme[12–16] and receptor biology.[17–21] By contrast very few departments of medicinal chemistry, pharmacology, or even chemistry offer a coherent course of study blending structure, chemistry, biology, and computational applications.[22] Industrial computational chemists as a result represent a wide distribution of theoretical and experimental backgrounds.

While a few firms currently operate with a single computational chemist, the majority have established CADD groups ranging in size from 5 to 20 scientists. Annual budgets for this research component fall in a window of \$0.5–3.0 million per year and represent perhaps 5–10% of the research dollar.[23] Hopes are high that the discovery of model therapeutic agents will be qualitatively and quantitatively influenced by computational activity. Less firmly established at present, similar computational groups operate in the agricultural and polymer industries.[24,25] In spite of the hope, it is possible to justify the following proposition.

At the level CADD groups are presently integrated throughout the pharmaceutical industry, there is little chance they will make a fundamental impact on drug discovery in the short term.

Medicinal Research Reviews, Vol. 11, No. 6, 641–662 (1991)

CCC 0198-6325/91/060641-22\$04.00

The basis for this statement is examined below. It will be argued that the major problems do not lie in software and hardware issues nor in the current state of our knowledge on how to apply these tools effectively. At the heart of the matter are two factors: (1) the organizational structure of research units presumed to incorporate or interact with CADD groups, and (2) the "mindset" of project teams employing computational methods as a discovery approach. In short, the considerable resources of highly talented CADD scientists are generally focused only indirectly on the central questions leading to new drug entities. A corollary to the above proposition can, however, be projected.

If management and synthetic chemists with decision-making responsibility commit to insuring a true, collaborative integration of CADD into the research process, the current peripheral emphasis can be redirected with potential major consequence for drug discovery.

This part of a two-article series is devoted to outlining the current situation experienced by most CADD groups in the pharmaceutical industry.[26] Attention is likewise given to describing what is technically possible. In the second part, further analysis leads to a series of recommendations for creating a research environment that attempts to establish the corollary as reality.

II. INTEGRATION OF CADD INTO DRUG DISCOVERY

Under ideal circumstances the CADD group is fully integrated into the discovery process as one leg of a tightly coupled three-way team [Fig. 1(a)]. Depending on the particular project, the "biologists" may be pharmacologists, biochemists, animal physiologists or genetic engineers. The technical skill offered by this component is usually the evaluation of bioactivity. However, protein expression and purification is becoming increasingly important. Most frequently the "chemists" are broad-based synthetic chemists, but they may reflect a more specialized focus in heterocycles, peptides, proteins, or carbohydrates. In any case, the technical contribution of this group is the preparation of specific compounds for biological testing. The third member of the trio, CADD, offers expertise in the manipulation of computer hardware and/or software and the construction of potentially predictive SAR models of varying degrees of sophistication.

Were the technical knowledge possessed by each member of the project team the extent of an individual's contribution, the endeavor would surely languish. A highly effective discovery effort requires that a dynamic process be established. The categories must overlap to some extent, as shown in Fig. 1(b). Each functional team member learns the language of the others suffi-

---

Dr. James P. Snyder received his Ph.D. in 1965 in synthetic organic chemistry from Cornell University. Subsequent positions at the Belfer Graduate School of Science, Yeshiva University, New York City, and University of Copenhagen, Denmark, permitted research into organic reaction mechanisms and molecular conformation. The work integrated both experiment and a range of computational methods. In 1981 he joined Merck Sharp and Dohme, New Jersey, as an internal computational consultant. Three years later he moved to Searle Research and Development, Skokie, IL, to head the Drug Design unit, where he is now both Head and Senior Fellow. Current research interests include approaches to receptor mapping, pseudoreceptors, excitatory amino acid mimics, enediyne antitumor antibiotics, and protein assembly antagonists.

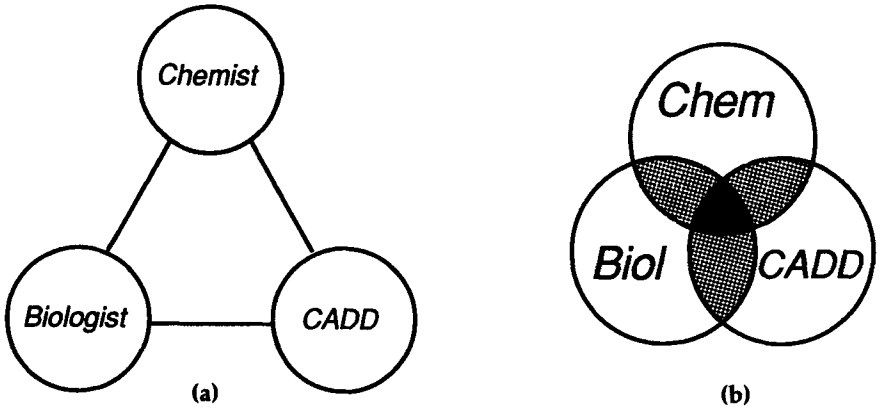

Figure 1. (a) Three functional components of a broad-based lead discovery project team; (b) Overlapping characteristics include responsibility, inventiveness, and the ability to mutually influence decisions across team boundaries.

ciently to evaluate the ongoing results. Furthermore, interaction is promoted whereby the developing research is critiqued—constructively—from each corner of the triangle.

For example, the bioassay in use might consist of an animal model with relatively slow turnaround time and a generic receptor assay. For more precise structural targeting the team could ask for redirection of resources to provide the development of a series of novel receptor subtype assays with high throughput. Similarly, the synthetic chemist might be encouraged to increase the structural diversity of a given lead series or to target specific compounds as part of hypothesis testing. The computer model from the CADD representative may be based on too narrow a set of structures, rest on weak assumptions, or fail to provide persuasive predictive insight. Project team members ought to be in a position to provide direction necessary for model refinement.

More succinctly, a strong and integrated project team is populated by goal-oriented individuals with a scientific sixth sense, a pragmatism that elicits decisions consistently favoring the common target, and a cooperative spirit permitting good-natured but substantive give and take. Synthetic chemists, biologists, and computational chemists each bring to the table an agile mind, a viewpoint, and a desire for team as well as individual success. The accompanying technical tools, while essential, are secondary to the wider landscape. Figure 2 illustrates a simplified depiction of the overall process.

Often, though not always, the "mechanistic concept" owes its origin to fundamental studies in pharmacology or biochemistry. Once the principle is enunciated, specific and novel structural targets can be designed. This may be accomplished by an intuitive analysis of available SAR. All team members should be capable of and willing to contribute to this exercise. At another level, computer-assisted model building can uncover nonintuitive patterns in the data and lead to novel structural suggestions. These, of course, need to be critiqued by synthetic chemists for preparative feasibility. A few conver-

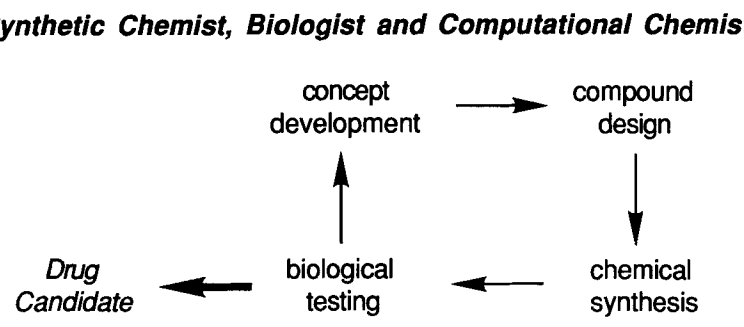

Figure 2. Steps in the iterative lead generation process ideally under influence by all team members.

sational iterations are usually sufficient for structural selection based both on the pragmatics of synthesis and faithfulness to the computer model.

The latter is always constructed on the basis of a series of assumptions, as is the case for intuitive SARs. Assumptions in the two approaches are, however, quite different. Instinctive conclusions are usually drawn from a 2D, connectivity analysis for a reduced subset of similar structures. The expectation is that the constrained partial stereochemical analysis contains enough information to accurately project desired properties for a novel structure. In contrast, while a computational excursion can rigorously cover 3D and other aspects of a large dataset, the methods employed may involve systematic limitations. For example, peptides calculated as gas-phase structures introduce severe conformational artifacts. Reliable solvent models readily applicable to large numbers of structures or conformations are only now becoming available.[27–29] Alternatively, electrostatic potentials derived from point charges provide unrealistic surfaces for lone-pair–bearing atoms.

Curiosity and Socratic-method on the part of synthetic chemists and biologists can illuminate pitfalls and serve the team well in developing the most robust and consistent computer model. Regular joint sessions in front of a graphics screen are an excellent means to share insights and to deepen one's understanding of the limits of the computational tools. Just as a mathematic-based model's predictions can benefit from careful scrutiny, so should intuitive suggestions from all quarters be subjected to filtration by the model. The degree to which the latter directs target compound planning will vary depending on the makeup of the team. Nonetheless, it is vital that a balance be struck. The highest priorities for synthesis are best decided as a team exercise where advocates for specific structures bring forth their proposals for all to evaluate. By the same token, time should be allocated for exploration of strong hunches independent of computer models. Serendipity remains an important method of lead evolution.[30,31] Once the priorities of the targets have been determined, the details of synthetic planning are ordinarily formulated by the synthetic chemist. This can be a demanding and highly creative exercise considering that proposed structures represent unknown compounds. Once again, however, broad-based knowledge within a team may be able to make useful and unexpected contributions. The lines of communication at this step are most profitably left open.

Table I
CADD Group Activities Important for Lead Discovery, R&D Support, and Maintenance of State-of-the-Art Computational Facilities

Visible	Invisible
Project team participation	Software M and E[a]
Short-term consultation	Method testing
In-house training	Method development
Demos/marketing activities	Hardware M and E[a]
Publication	Distributed processing

[a]*M*aintenance and *E*valuation

Finally, testing of the compound is accomplished by the biological wing of the group according to a mutually acceptable protocol. Since the resulting data form the backbone for decisions to be made by all team members, it is wise for nonbiologists to have paid a visit to the laboratory at some point to experience data collection. The predictability of intuitive or computer-based SAR models depends to a large extent on the precision and accuracy of the bio-data. This varies considerably with animal model, type of tissue or cell preparation, and purity of a protein extract.

To circumambulate once about the cycle depicted in Fig. 2 is not enough. The ultimate research alert will result from multiple, iterative passages and probably involve other disciplines as well. In some cases, a protein x-ray crystallographer, metabolism expert, or a toxicologist may sit among the team members. *As the drug candidate is refined, a well integrated project will provide the opportunity for timely involvement of team members in all stages of the refinement cycle.* The challenge to folding CADD into this scheme is two-fold.

III. MULTIPLE ROLES OF CADD PRACTITIONERS

A balanced CADD group with the widest range of capabilities wears a number of hats. Some activities are "visible," others "invisible" to most colleagues and managers in the immediate pharmaceutical environment. Both categories require manpower and resources. Table I provides a list of important responsibilities.

First and foremost, a fully utilized CADD unit enjoys full collaborative membership on the discovery project teams. This implies that a CADD scientist studies the etiology of a target disease, develops some understanding of the supporting biology, and becomes familiar with the outline of the synthetic strategies. Responsibility is taken for assimilating the major multidisciplinary outlines of the project so as to optimally deploy the individual's structural and physical chemical expertise. A long-term commitment to a project is clearly required. At Searle, CADD personnel are individually limited to two active discovery projects. As the research evolves, the computational specialist is obligated to develop predictive models, present them regularly to project colleagues, and make specific structural proposals coincident with the project team's goals. As the interactive interplay unfolds, the CADD scientist is expected to demonstrate a qualitative impact on the direction and priorities of the project team.

Short-term consultations can involve graphics presentations, a one-time

modeling study, or blackboard brainstorming.[32] Training comprises introduction of chemists and biologists to the use of PCs, introductory elements of certain software packages, and familiarity with graphics display. An average of biweekly presentations to visitors and company colleagues consumes a considerable amount of time for scheduling, preparation, and the actual demonstrations themselves. Occasionally, an intimate working relationship with marketing or an advertising firm can be expected to assume the proportion of a short-term project. Finally, the opportunity to publish presents itself both in terms of cross-discipline research application and method extension or development. In a number of pharmaceutical settings, establishing a presence in the literature is not only encouraged but expected as one of the conditions for career development. Other visible activities may include university networking, new project proposal evaluation, interdisciplinary job candidate interviewing, and interaction with the media.

On the invisible side of the ledger—about 30–50% of the group's time—is the effort that permits the CADD group to maintain state-of-the-art status. In the current late 1980s–early 1990s environment, major software packages often incorporating new methodology are generally purchased from commercial vendors. These are now generally second or third generation, sophisticated and expensive ($50,000–150,000). Still, no commercial house can anticipate all the needs of a given applications' environment. It remains necessary to treat problems specific to a given research project and to locally extend known methodology. This means that new capabilities delivered in advanced versions of commercial software need careful evaluation. On the one hand it is critical to establish consistency of the code with published experimental data as well as its suitability for in-house problems. Failure to exercise this element of quality control can seriously compromise anticipated application. In the event that a project problem is either inadequately addressed by marketed software or outside its scope, the CADD group is required to carry out its own development. This implies writing the computer program from scratch, testing and debugging it, and integrating the new tool with existing in-house software. Few groups have managed to avoid this obligation.[33–38] Often an industry-university alliance can shorten the development process.[39–41]

Equally demanding in the current atmosphere is keeping abreast of the rapidly growing range of hardware options. Very fast PCs, powerful graphics-enhanced workstations, parallel computers such as the Intel Hypercube and supercomputers with advanced vector facilities complicate both scientific and economic choices. Software may not be readily transportable between these machines, yet selection of a problem-solving strategy often depends on machine throughput. Can I get the answer in an hour, or must I wait three days? Do I settle for a model far less robust than possible in the interest of timeliness and budget considerations? Certain approaches and problems are simply inaccessible without access to the larger computers. An informed CADD unit, even with very supportive relationships with the Systems and Information Services groups, needs to stay on top of these issues—issues in rapid fluctuation.

Finally, the category of Distributed Processing places three separate pressures on an eclectic CADD group. First, no single piece of software is ordi-

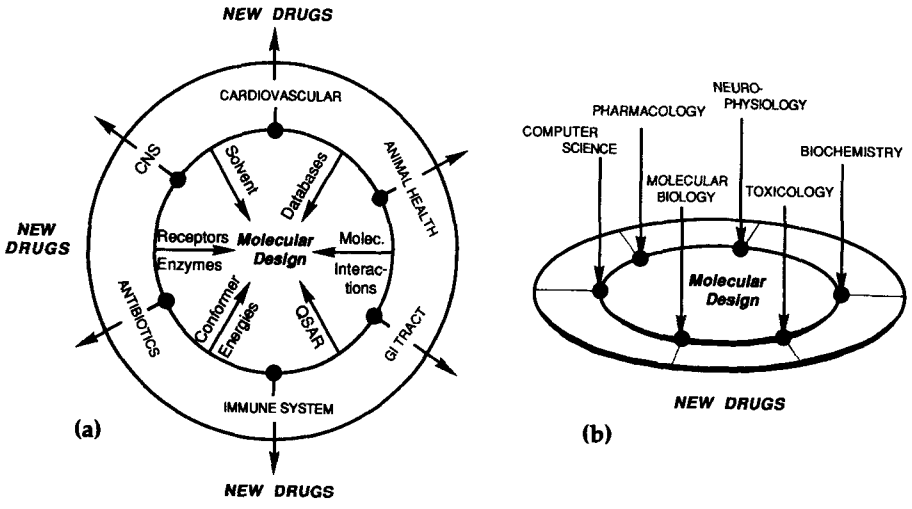

Figure 3. The discovery milieu as seen from the vantage point of the CADD group. (a) The inner circle represents maintenance of small-to-macromolecule technical expertise; the outer, project application. (b) The impact of other fields on project work.

narily sufficient to address a routine but multistep modeling task. For example, conformation generation, optimization, and least-squares fitting can involve three separate computer programs. The XYZ coordinate output from the first is the input for the second; output from the latter is input for the third. With an evolving library of 40–50 active codes, the task of assuring comprehensive and smooth coordinate interconversion is a demanding and ongoing one. Second, if the environment includes a network of different computing platforms—for example, DEC VAXs, a Silicon Graphics workstation, an IBM 6000, and a Cray supercomputer—the applications programs will need to operate on a user-determined selection of these. Transporting the software from the VMS (VAX) to the UNIX (Silicon Graphics/Cray) operating system is a nontrivial exercise. Likewise, moving between common operating systems (Silicon Graphics → Cray) can consume considerable resources, particularly if special machine features such as vector or parallel processors are to be utilized to the utmost. Third, the existence of several hardware types in the computing network necessitates a seamless transfer of input and output across machine-machine interfaces. While existing software is available to assist the work, it almost always needs tailoring and enhancement in the establishment of an individual environment.

To summarize, the CADD group is obligated to encompass a wide range of technical and intellectual talents in order to deliver predictive models in a timely manner; to let the project team problem determine the choice of computational method. This contrasts with the all too frequent situation whereby the availability of limited software and/or hardware or previous personnel training causes a narrowly defined approach to reshape the problem along less productive lines. Figure 3 presents one view of the multipolar environment as seen by a CADD unit. Internally, an array of talents is shared in

order to be able to address the widest possible range of physical phenomena. Externally, each group member proceeds along a separate line responding to the project team and its specific therapeutic endpoint. The attributes of an individual hoping to impact drug discovery in this milieu obviously cannot be narrowly focused.

IV. EXPECTATIONS FOR CADD IN THE 1990s

Under ideal working conditions, what can a well endowed CADD unit actually contribute to drug, fungicide, herbicide, or pesticide discovery? There are two major factors that influence the efficacious delivery of computational methodology to the discovery process. One is scientific; the other, human-relations oriented. Although they are inextricably entwined, two assumptions are made in this section to tease them apart and to emphasize the purely scientific aspect. The first is that management has solved the political problem of fully integrating CADD into the collaborative scientific process. Secondly, the CADD unit has developed sufficient maturity and material resources to address the complexity of molecular design issues arising within a talented and goal-directed project team with a deadline. At present, these assumptions rarely hold, but there is good evidence that the pharmaceutical and agricultural industries are moving gingerly in this direction. The assumptions are addressed in subsequent sections.

Table I presents a variety of the central responsibilities of a typical CADD group. The lifeline of a company, indeed the industry as a whole, resides in the first visible function: *Drug invention through project team participation.* Frequently, but not exclusively, the design task facing a therapeutic team follows a different path, depending on whether the microscopic receiver protein is structurally characterizable or not. For the sake of discussion, we take by turn excursions through hypothetical AIDS and CNS programs. While the case histories are fictitious, the details have been drawn from actual project team activities.

A. An Integrated Approach to Enzyme Inhibition

The life cycle of the HIV-1 retrovirus considered to be the cause of AIDS is now known in considerable detail.[42] Once a virus particle invades a healthy cell, its previously well protected RNA and the accompanying reverse transcriptase enzyme promote a cascade of events. Among them is the production of several proteins and enzymes which support reproduction of the virus as it commandeers the machinery of the host cell. Molecular biologists have decoded the sequence of one such enzyme, a 99-amino-acid HIV-1 protease, and by recombinant DNA techniques are producing quantities for use in bioassays and x-ray structure analyses. For the purpose of the present discussion we suppose that the AIDS team has decided to target specific inhibitors for this enzyme; a formidable task, because the eventual compounds need to penetrate the cell wall membrane during viral reproduction. Where do the CADD scientists begin? The following is a typical scenario written in late 1988 prior to publication of the early HIV protease structure work.[43,44]

The experienced computational chemist and project team colleagues know that a great deal of modeling work has been carried out in an effort to inhibit

proteases in the field of hypertension.[13–15,45,46] A series of ACE and renin inhibitors are therefore investigated as test inhibitors for the HIV-1 enzyme. One or two of these are moderately active. This reveals that the active site of the HIV-1 protein resembles that of ACE, renin, and a family of proteases for which detailed three-dimensional x-ray structure information is available. Using principles of structural homology,[47] intuition, and a flexible computer graphics package, the CADD scientist compares[48,49] the sequence of HIV-1 protease with that of known 3D aspartyl protease structures and folds the primary sequence of the AIDS protease into a reasonable 3D model. The work requires considerable modeling experience and a high degree of hands-on manipulation to formulate a dimeric structure consistent with biochemical evidence and to complement the α-carbon protein backbone with appropriately placed amino acid side chains. Nonetheless, the putative active site proves compatible with a limited SAR and the family of related proteases. It is noteworthy that computer programs based on database searching,[17,18,21,36–39] neural nets,[50] and artificial intelligence are emerging that promise to make 3D protein construction from primary sequence at least semiautomatic within the middle to late 1990s.[51]

The team calls for the synthesis of additional potential inhibitors to expand the SAR, a cleaner enzyme preparation for accurate measurement of inhibitor binding constants (K_i's), and greater quantities of the enzyme for structure determination. With only 99 amino acids in the HIV-1 protease both NMR and x-ray spectroscopy can be applied to the task. Furthermore, a recently developed x-ray structure refinement program based on molecular dynamics can speed structure definition in the final stages.[52] It resides on a supercomputer. The CADD and protein x-ray crystallography groups will work together in an attempt to achieve an ultimate 1.8 Å resolution for the enzyme.

Meanwhile the CADD scientists dock the best antihypertensive inhibitor in the active site of the folded protein model. Presently a laborious graphics-based task, the docking procedure is under revision by the CADD group for both increased speed and precision. The computer chemists surround the complex with water using a "soaking" protocol devised under a university contract. The entire assemblage is subjected to geometry optimization by means of a molecular mechanics calculation. The detailed inhibitor-protein interactions are analyzed by computer graphics to show a coiled inhibitor structure encased by six hydrogen bonds and one significant hydrophobic contact. In collaboration with the synthetic chemists, several novel structures accommodating these forces are designed to fit the model protein complex active site pocket. The chemists, in addition, incorporate several structural features consistent with their multistep synthetic scheme. The compounds are made and tested for inhibitor activity. Only one target shows a significant increase in potency, but its activity still falls into the micromolar range. The model is refined by side-chain relocation and new inhibitor candidates are designed by the team.

Meanwhile, the enzyme x-ray structure is solved. The side chains of two amino acids in the folded model were incorrectly placed as a result of dimer misalignment. The synthetic and computation chemists refine the latest inhibitor design by conceiving three novel variations. They are ranked by several protocols. The first is goodness of fit based on the structures of the geometry

optimized complexes. The second, free energy perturbation,[53] requires use of a supercomputer. In favorable cases the method can predict relative K_i's. During the course of the work it points to one structure as particularly promising for high potency. Thirdly, several intuitive suggestions that fall outside the province of the model are persuasively presented. The entire team sets synthetic priorities and the cycle depicted by Fig. 2 is traversed until a selective inhibitor with nM potency in the binding assay is obtained.

Unfortunately, the best inhibitor shows marginal passage across the membranes of the HIV-1 whole-cell assay and simultaneously demonstrates poor availability in monkeys. The CADD group contributes to an understanding of the former by constructing a computer-based membrane bilayer model. The compound's facility to cross the bilayer is studied by molecular dynamics and log P calculations. The work illustrate a need to develop a new procedure for estimating log P's for flexible molecules. Meanwhile, the metabolism group learns that *in vivo* cleavage of two amide bonds in the lead inhibitor causes the low bioavailability. Suitable amide bond replacements are suggested; one is rejected, because it prevents the inhibitor from adopting a suitable conformation at the enzyme active site.

A second iterative passage around the cycle of Fig. 2 leads to a novel, potent, and bioavailable compound that penetrates and kills HIV-1–infected cells. The compound moves into Development as phase-one clinical trials are planned for the new drug.

Comments

The HIV-1 protease project team sketch describes close collaboration among six separate groups (synthesis, pharmacology, molecular biology, CADD, protein x-ray crystallography, and metabolism) to achieve early clinical trials. Written with emphasis on CADD contributions, the group is depicted to have cross-correlated AIDS and hypertension, provided a predictive early enzyme model, supported the x-ray crystallographers, codesigned a variety of prospective inhibitors, aided in the resolution of bioavailability and metabolism issues, influenced team decisions, and developed several novel computational tools. A similar range of contributions could be listed for the other groups involved. As described, the final compound would be hard to identify as a CADD-only compound. At the same time it would be difficult to dispute that the CADD group had made seminal input to the overall discovery process and, consequently, to a reduction in research time leading to development.

In actual fact the intimate linkage between drug targeted disciplines has moved with incredible speed. Although HIV-protease was recognized as a point of viral intervention in 1988 and early 1989 when the above was penned, neither 3D protein structure nor serious inhibitor candidates were then identified. In the intervening two to three years the native enzyme has been prepared both by laboratory synthesis[54] and recombinant DNA technology.[55–57] X-ray crystal structures of the native enzyme[43,44] and a growing number of enzyme-inhibitor complexes are now available.[58,59] In turn, these spatial representations have been instrumental in the design and synthesis of potent peptidic,[60,61] peptidomimetic,[62–64] and nonpeptidic[65] blockers of both HIV-1 enzyme and virus-infecting whole cells. One of these is undergoing

clinical evaluation.[63] The intimate details of recent and actual HIV-1 inhibitor invention obviously vary from those phrased above. Nonetheless, it is clearly possible to foresee the influence of integrated CADD practice on the development of potent and selective drug candidates.

B. Iterative Strategy for Receptor Modulation

Another qualitatively different vignette involves cell surface receptors. In this situation the CADD representative again works primarily in a triad with synthetic chemists and biologists, but information on the molecular structure of the receiver protein is completely unknown. This problem orientation is presently the norm for most pharmaceutical drug research teams. In the future, cloning, expression,[66,67] and crystal structure determination[68–71] of receptor protein can be expected to provide molecular detail in this context as well.

A project team previously constituted for research in antipsychotic drugs is informed of a recent report on the discovery of a hitherto unknown serotonin receptor subtype, 5-HT_x. The latter appears to mediate the manic phase of the bipolar manic-depressive illness. As no mechanism-based drug for this condition is known, the team is directed to seek a selective antagonist. The literature report presents binding data (K_i) for 25 serotonin receptor ligands to the 5-HT_x receptor in addition to the related serotonin subtypes, 5-HT_{1a} and 5-HT_2. A novel antagonist series labels 5-HT_x unambiguously, but there is considerable crossover. The project team target is a potent and selective 5-HT_x antagonist within 18 months time.

The CADD team member recognizes the problem as one requiring the construction of several mutually exclusive receptor models for closely related compounds. In a previous collaboration with the GI-anti-ulcer team, the same problem arose in a different context. Elimination of side effects from the ulcer-preventing drug candidate was the task. Accordingly, the construction of nonoverlapping, multiple receptor models assisted in suppression of diarrheagenic effects while retaining antisecretory potency.

The team's work begins with the development of a functional physiological assay and synthetic exploration around the previously reported lead antagonist. At this early stage, an analysis of the molecular structure of the latter by CADD and the chemists suggests three deep-rooted structural modifications that should assist in the definition of the receptor-active conformation. In particular, biological data for several chiral, rigid and cyclic analogs is presumed to furnish a maximum of SAR insight. The synthetic work required to prepare the cyclic derivatives in question is substantially greater than that demanded of the classical substituent approach. The team believes, however, that the greater the degree of information elicited early in the project, the richer the dividends in later phases. Part of the synthetic team addresses sterospecific routes to the cyclic compounds; part, analog synthesis.

The CADD chemist then turns to the SAR of the 25 conformationally flexible ligands. The three most selective at 5-HT_x are subjected to a full conformational search leading to a total of 9,000 molecular shapes. These are best geometry optimized on a parallel computer programmed with commercial software. The local 32-node Intel Hypercube performs the task overnight. The resulting

structures are intersected for certain elements of commonality leading to five equally valid receptor pharmacophores. The conformational analysis is repeated, this time for three of the least selective 5-HT_x ligands. Data intersection permits elimination of two of the receptor model options.

Because synthesis of the cyclic targets is still underway, a computational scheme for further conformational refinement based on molecular volume is conceived. The computer code is written and tested. Applied to the problem, another of the receptor pharmacophore alternatives is eliminated. By this time a set of analogs and one of the cyclics have been submitted for testing in the binding assay. The results tentatively reduce the 5-HT_x pharmacophore options to a single choice. The CADD and chemist subteam thereby develops a new molecular design bypassing the need to synthesize one of the previously chosen cyclic structures.

At this point, the second pharmacophore mapping phase is begun. Complementary receptor models are constructed for the 5-HT_{1a} and 5-HT_2 subtypes based on several sources of literature data. The 3D projections of the three 5-HT subtypes are clearly different. It becomes evident as to why the original lead 5-HT_x antagonist is only partly selective. The second pass design appears to avoid certain features of the antagonist responsible for its ability to fit more than one receptor model. Synthesis and testing of the first members of this series indeed show increased but insufficient selectivity.

Returning from a conference on receptor biology the CADD team member describes the report of an entirely new compound class that binds to the 5-HT_x receptor subtype. The university scientist who conducted the research has agreed to submit his compounds for in-house testing. A consulting contract is subsequently established. The new structures stimulate a qualitative refinement in the 5-HT_x receptor model. In light of the improved hypothesis for the receptor active site, the synthetic chemists suggest a hybrid third-pass series incorporating the earlier design and the new structural feature. Iterative design and synthesis continue with a structurally oriented biologist making a further selectivity-enhancing suggestion. The novel insight arises from the recently established in-house electrophysiological assay, which parallels the binding studies in every way with the exception of two key outliers. The latter catalyze the new proposal.

At the end of 18 months a novel, a patentable antagonist has emerged. Potency is moderate, but the selectivity ratio has gone from 5-HT_x/5-HT_{1a} = 2.1 and 5-HT_x/5-HT_2 = 6.5 to 390 and 850, respectively. The compound is submitted for toxicity and metabolism evaluation.

Comments

As in the HIV-1 protease work, the project team has been portrayed as a highly interactive and mutually supportive group of scientists. The final development candidate is clearly a compound incorporating contributions from all three points of the triangle (Fig. 1). As the narrative is presented, the CADD scientist has provided a semiquantitative three-dimensional scheme for enhancing selectivity. The entire team has refined its properties through successive stages to an acceptable and proprietary endpoint. The CADD team member, in addition, has demonstrated a strong commitment to project goals by providing highly relevant new information from the outside and, ulti-

mately, a contributing consultant. The challenge for management is creation of an environment where such commitment is commonplace within a talented, ambitious, and multidisciplinary team.

V. TIMING OF CADD'S INVOLVEMENT IN DRUG DISCOVERY

The history of CADD in the pharmaceutical industry provides no strong precedent for choosing the optimum point in a project's life when the practitioners of computational methodology should be engaged. The decision is usually dictated by the availability of CADD resources, interest on the part of project team members, and the assertiveness of middle to upper management. In actual practice both newly initiated projects as well as those of long standing have profited from CADD thinking. There is, however, a characteristic common to all product-oriented research groups that employ this technology for lead-seeking advantage; namely, compound synthesis.

As indicated in Table I and the accompanying text, the primary activity of CADD is the design and proposal of novel chemical entities as concept tests and research leads. Traditionally this activity has fallen exclusively to the synthetic chemist. Decisions have generally been reached on the basis of intuition, analogy, and qualitative SAR followed immediately by synthetic follow-up. This, in fact, is the purpose of synthesis: to provide the research pipeline with novel and proprietary substances as drug candidates. The principle that governs the timing of CADD involvement, then, is this:

> If the project employs synthetic chemistry for lead or analog development, CADD can be of assistance in shortening lead time and enhancing desired biological properties.

The means for designing an unknown molecular entity and making a choice to bring it into existence always involves the mental process of model building. This applies at the most naive intuitive level as well as to conditions where the 3D coordinates of a target enzyme are in hand. The contribution of CADD is easily appreciated near the latter end of the spectrum as illustrated by the HIV-1 protease effort sketched above. Much less appreciated is the potential for contributing at the earliest possible phase of a project as synthesis is first being contemplated.

The problem of preventing blood clots (thrombosis) by inhibiting platelet aggregation offers an opportunity to exemplify the above proposition. Let's assume the cardiovascular group discovers either in the laboratory or in the library that a single compound of unexpected structure suggests remarkable potency as an antithrombotic. Traditionally, several chemists might be assigned to make a series of straightforward analogs to broaden the structural base. By contrast, involvement of an experienced CADD scientist at this point may have several important consequences on the team's early thinking. Not least, the CADD person can draw on SAR patterns observed in other therapeutic areas which may be of immediate relevance to the biological action of the unexpected structure. Substances that prevent platelet aggregation, for example, bear a cause-and-effect resemblance to agents that promote cell degranulation during inflammatory processes. Both are receptor-mediated events. Recognition of similarities can provoke novel avenues of exploration. Informal sessions among team members can raise mechanistic questions around

issues of conformation and reactivity and thereby impact contemplated molecular modification. For example: Does the lead compound resemble protein patches thought to mediate platelet aggregation? Are the sulfhydryl groups (—SH) on proteins that regulate thrombolytic events compatible with the contemplated compounds? Even simple synthetic alteration can be designed so as to elicit a maximum of subsequent SAR information in the absence of mechanistic insight. The effects of substituents that induce steric, electronic, log *P*, and pKa variations are well understood. If judiciously chosen, the preliminary set of compounds can explore the widest range of physicochemical phenomena in response to bioassay, while requiring a minimum of synthetic effort. Simultaneously the stage is set for subsequent in-depth model building. Many early "shotgun" efforts neglect this point altogether. Furthermore, while early conceptual thinking may not involve extensive computation, it can broaden the mindset of project team members and provide a common understanding of the problem from the very start. Other factors may dictate deployment of CADD resources, but opportunities can and should be exploited at the onset of chemical synthesis in a lead-seeking project.

VI. IMBALANCE IN THE TRIANGULAR RELATIONSHIP

Suppose CADD personnel were assigned to a therapeutic project team, furnished with state-of-the-art computational tools, provided with headcount sufficient to span the critical technical disciplines, and given regular access to monthly proprietary research reports. While these conditions are minimal for performing molecular design studies on relevant drug candidates, they by no means guarantee that CADD can influence drug discovery in a meaningful fashion as implied in the idealized sketches above. The reason for this is embedded in Fig. 2, a flow of events from concept to practice accompanied by cyclic iteration. It has been implied that a triangular set of interdependent relationships (Fig. 1) underpins smooth iterative passage until predetermined riteria are satisfied. What is not immediately evident is that the three-way interaction incorporates qualitatively different interdependencies. If CADD were eliminated from the project team, the biologist-synthetic chemist interaction still permits discovery-active movement around the cycle, accompanied by lost advantages such as shortened lead development time, semiquantitative structure prioritization, molecular precision, and sophisticated 3D thinking. In fact, this represents precisely the situation prior to introduction of CADD to the industry during the last decade. Elimination of either biologist or bench chemist points on the triangle shuts down the discovery process. In other words, only two of the three possible pairwise relations in Fig. 1 contain the resources minimally necessary to pursue drug discovery. The resulting imbalance in the multidisciplinary dependence among research peers has a variety of deep-rooted consequences.

One fundamental outcome of the imbalance is the decision, often made unconsciously, to utilize the CADD team for all activities given in Table I *except* for effective project team participation. This can be understood by recognizing that in the most highly evolved research unit only two of the triangular partners, synthetic and computational chemists, routinely engage in a common and singularly focused creative act: molecular design. Yet only one of the pair controls the resources to bring a mental construct into existence.

In the absence of a completely cooperative research milieu, the CADD scientist within a project team is obligated to negotiate his ideas into practice. Without line responsibility or integration, the CADD unit is relegated to the role of consultant. This means responsibility without authority and, ultimately, without credit. No similar constraint operates for either the synthetic chemist or the biologist whose scientific loops are closed by access to operational experimental facilities. Few practicing scientists are vested with the requisite skills and the patience to consistently employ persuasion as a condition for investigate closure. Following the inclinations of human nature, where persistent barriers obtain, most workers simply withdraw to more satisfying work while maintaining credibility elsewhere.

The true state of affairs is not readily perceived by middle and upper management. Across the industry a project team as a whole is usually obligated to furnish one compound per year for potential development. A few of these almost always appear highly promising and therefore justifiably create an aura of "research success." At the same time the CADD unit can be productively visible in a variety of ways (Table I). CADD team members are often accomplished Ph.Ds who carry out excellent, but not necessarily drug-targeted, science. In view of these conditions against the backdrop of a busy and complex pharmaceutical bureaucracy, the fact that a CADD group is not primarily discovery-oriented can go unnoticed. A prime example is the innovative modeling system established at Merck in the late 1970s,[33] but deployed routinely by the talented CADD group only in the late 1980s.[12]

The imbalance described above has other immediate consequences as well. If part of CADDs mission is indeed drug discovery, the failure to consistently obtain synthetic follow-through and iterative refinement of an idea compromises the most valuable potential of molecular design. In such a circumstance, the scientific loop remains open and no test of the validity of the CADD approach is performed. Beyond personal frustration, the computational methods in such an environment remain frail, valuable experience is lost and major lines of drug discovery are weakly influenced, if at all. From a comparative viewpoint, tolerance of a marginally influential CADD group not only makes the company less competitive in the marketplace, but it also promotes a progressively weaker position for the future.

The search for and maintenance of CADD talent is likewise impacted by the metastable state between the tripartite partners of Fig. 1. While scientific managers are empowered for possession of a range of qualities including leadership, bench scientists are chosen primarily for scientific or technical excellence. Though a practicing scientist must be judged able to "fit in," polished human relations skills are generally regarded as secondary. Effective, discovery-oriented CADD scientists, by contrast, are best screened by a more complex standard (see below). Likewise, in the current atmosphere it may not be possible to measure their performance by the same yardstick as applied to the working synthetic chemist or biologist.

VII. THE CURRENT ATMOSPHERE

What are the prospects for members of a CADD group committed to collaborative drug discovery in the pharmaceutical industry as the 80's turn to the 90's? The answer depends on many factors including the unit's experience

in the industrial matrix, the number and talents of its members, the leadership abilities of its head and the attitudes of middle and upper management. On average, however, it would appear that about one-third of the CADD projects approach the level of interactive excellence reflected by the HIV-1 protease and Manic-Depressive programs highlighted above. One-third involve marginal to moderate impact by CADD on the leads which move into development. The final third of the projects supported would appear to result in little or no impact.[72]

The less than ideal condition implied by the latter two categories stems from several sources, a few of which will be touched on in outline here. In the first place, the last 15 years have seen drug discovery move from a chemistry-driven phenomenon to a biology-driven one; from intuitive structure alteration to a concern for biomechanism. In concert, the previous generation of chemistry-trained research managers has been largely supplanted by biochemists, enzymologists, pharmacologists, and M.D.'s. This transfer of authority is still a part of the career experience of a high percentage of active industrial synthetic chemists.

Secondly, the practice of awarding patents to the inventors of drugs, a protective necessity for pharmaceutical firms, has been institutionalized by management in the form of public announcements, awards ceremonies and other means. While the credit is clearly justified, the waves of commendation travel only a short distance. The vast majority of patent holders are chemists. Understandably the awards become a part of a scientist's career and publication record. Patent authors are cited for both invention of the idea and its reduction to practice. It is the former that is one province of CADD and biologists with a structural disposition.

The practice of recognizing patent awardees is innocent enough on its face. However, the public ritual operating in some companies underpins the potential career bonanza with the proportion of myth. The identification of an individual synthetic chemist with an FDA-approved blockbluster drug is a medicinal chemist's equivalent of winning the lottery. In corners of the industry names such as Robin Ganellin and Graham Durrant (cimetidine/ulcers), George deStevens (thiazides/diuretics), Miguel Ondetti and David Cushman (captopril/hypertension), Frank Colton (progesterones/birth control), T. Y. Shen (sulindac, indomothacin/NSAIDS), Leo Sternbach (benzodiazepines/anxiety), Paul Janssen (haloperidol/psychosis, diphenoxylate/diarrhea, cinnarizine/allergies, alfentalin/anesthesia . . .), Robert Morin (cephalosporins/antibiotics), Robert Mazur and James Schlatter (aspartame/artificial sweetner), and Paul Collins (misoprostol/ulcers) are legendary. To be sure, a select group of nonchemists have likewise been individually singled out for their far-reaching contributions. Frederick Banting and Charles Best (insulin/diabetes), Howard Florey and Alexander Fleming (penicillin/antibacterial), Selman Waksman (streptomycin/antibiotic), Gertrude Elion and George Hitchings (cancer, infectious diseases), James Black (propranolol/hypertension, cimetidine/ulcers), Jonas Salk and Albert Sabin (polio vaccine), for example, represent this elite group. Each of these scientists either discovered, synthesized, or isolated the ultimate drug for the first time, closely managed its preparation, or unraveled key elements of the biological mechanism of action. Most are likewise patent-holders.

The competition and ambition spawned by the hopes of extraordinary rec-

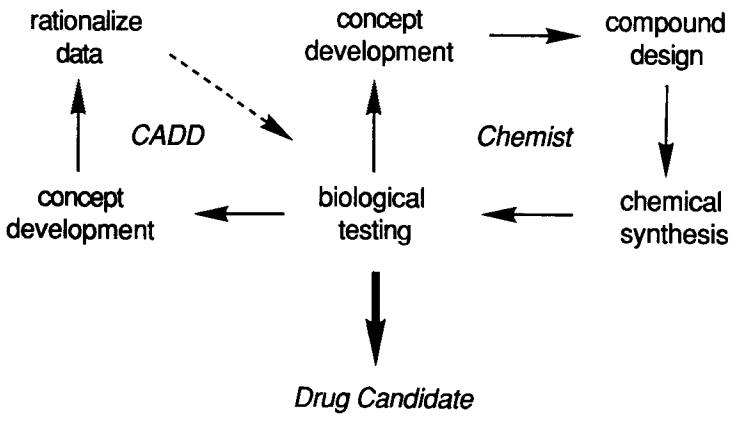

Figure 4. Parallel iterative cycles in which computational scientists play retrospective rather than prospective roles as concept inventors.

ognition is a vital element in the drug discovery process. However, when these aspirations are located forcefully in only a fragment of the discovery team, when the new technology (CADD and molecular biology) converges with the old during the creative act and when the newcomers are obligated to bargain for scientific fulfillment, conflict naturally arises. The individuals mentioned above, prolific though they have been, worked to create novel drugs in large and mutually supportive discovery teams. Subsequent development, clinical trials, registration with government agencies and marketing activities carried out in separate team frameworks were likewise essential for ultimate commercial success. In spite of the multitude of intellectual contributions necessary to accomplish the latter, the human need to simplify by generalizing coupled to classic mechanisms of credit distribution assure that distinction for the few represent the labors of many. When the operation of these principles is perceived during prepatent phases, traditional expectations can become counterproductive. That two-thirds of the CADD-supported projects yield moderate to little impact is one indicator that technology-merging in this area is not yet mature.

How does the situation manifest itself among working scientists? As outlined, one-third of the projects enjoy a high quality of inventive cooperation. Novel structures are considered to be the fruit of joint effort. Within the bottom one-third, the CADD scientist experiences at times overt resistance. Blackboard and computer sessions are few and unwelcome. CADD may not be invited to strategy planning meetings. Compound synthesis often begins and proceeds without first advising the full project team. For the sake of "finishing" the synthesis, fewer resources are available for other proposals. Synthesis priority lists—when constructed—are subtly reevaluated. Not infrequently, this takes place by the creation of a dual prioritization scheme whereby the potential of the latter targets are evaluated by a different set of criteria than those coming from CADD or biology. A not uncommon outcome is the situation depicted by Fig. 4, a derivative of Fig. 2. The CADD team member is shifted to a parallel cycle whereby his influence has been deflected to the status of rationalization. In fact, the shift is sometimes welcomed within CADD. Computational tools are much more safely applied in this arena. The

CADD scientist is credited with valuable "understanding." The tension invoked by moving too close to the creative act is avoided and the inevitable personal risks associated with prediction based on modeling are sidestepped.

In short, a practice in certain project teams is to reserve compound preparation resources for targets defined primarily by those who perform synthesis. Since the evaluation of hundreds of compounds is ordinarily required to produce a drug candidate in research, the dilution factor works nicely to the latter's advantage. A few "outside" suggestions can be explored without compromising the mainlines of inventorship. The traditional theme of patent distribution is protected, as is any credit assignment in the event of a drug discovery breakthrough. Not unexpectedly, in the middle one-third category, a blend of the two extremes is found.

To make maximum use of drug discovery resources in the multidisciplinary, pharmaceutical research environment, nothing short of a change in the culture is required. Similar arguments can be made for the agricultural industry as well as for the emerging synergism between molecular biologists and traditional pharmaceutical research scientists. The change can be catalyzed by awareness among line managers, attention to the qualities of the new-hires, adjustments in performance expectations, and a reevaluation of the credit distribution system. Aspects of these points will be addressed in the second part of this series.

VIII. DESIRED QUALITIES OF CADD SCIENTISTS

Promotion of the highest quality, long-term, multifaceted discovery environment requires judicious selection of CADD personnel. This is of special importance in view of the ongoing transition experienced by the participants in the triangular relationship described in the previous section (Fig. 1). Research talent is essential. Key characteristics include

Scientific excellence,
High computer literacy,
Familiarity with the language of organic and medicinal chemistry,
Willingness to learn and work in new fields.

Much can be said about the formation of a well balanced CADD unit to cover the extent of knowledge capsuled in Fig. 3. Obviously expertise with both small and macromolecules is needed. Quantum chemistry, force field methodology, and physical bioorganic chemistry must be represented. Experience in the principles of modern organic synthesis is extremely useful. Whatever the background of the candidate, however, the individual must be a superior practitioner with a parallel love for expressing and exploring ideas in the medium of the computer.

In the project milieu where structural design coupled to synthesis is pivotal, a candidate will be isolated unless able to communicate well in the language of organic chemistry. This means the knowledge of compound classes, trivial names, medium ring conformation, reaction types, and a reasonable ability to see and sketch in three-dimensions.

Equally important, the candidate must be prepared to significantly supplement specialized training with study in drug-related areas. Medicinal chem-

istry and pharmacology are essential fundamentals. The circumstance where one may be involved in projects from two or more quite separate therapeutic areas is demanding. Intimate familiarity with the significance of SARs from different *in vitro* and *in vivo* bioassays is the passkey to influencing project team direction. In addition, one quickly discovers the need to work at times with principles of toxicology, metabolism, genetic engineering, immunology, clinical investigation, marketing and corporate economics. Only an open and flexible mind capable of quick-study can meet the complex scientific challenge.

The talents enunciated above are those required as a basis for success at virtually all interfaces between disciplines. They apply without reservation to the three-way connection signified by Fig. 1. In addition, as a result of the interdependency imbalance implied by the same figure, CADD scientists are wisely chosen for additional personal characteristics as well.

Robust self-confidence,
Articulate communication,
Implacable sensitivity,
Independence with strong orientation toward collaboration.

A quality approaching unshakeable self-confidence is vital for the job. To be truly imaginative in the discovery process—occasionally provocative—calls for a willingness to make predictions based on incomplete models. There is considerable risk of failure in this endeavor even in a cooperative atmosphere employing iterative methodology. To be vulnerable in this manner among strong, competitive, and ambitious peers requires a very stable personality. At the other extreme, confrontation of rejection and hostility at times can test the limits of the most well adjusted individual.

Very helpful in the fast-moving team milieu is the ability to articulate clearly one's thoughts and to rephrase points in terms that other team members can grasp quickly. The obligation to persuade in order to accomplish scientific closure necessitates the exercise of patience, perception, and the lack of ambiguity. Attention to the hidden agendas of colleagues provides opportunities that are frequently missed by promotion of dogmatic, but fully supportable arguments.

Last, but by no means least, the CADD member must strive to become a master in the art of sharing. Completely open-ended collaboration is the goal. This applies to partly conceived ideas, incomplete computational studies (the status of all research!), as well as polished documents. In the dynamic setting of team research, timing is often critical. On-the-run decisions can cause unexpected changes in the course of a project. The greater access team members have to the full flow of information, the better equipped they are to deal with the change. Likewise, from CADD's perspective, the greatest opportunity for influencing a project results from shared ownership of the current computational model and the team's common understanding of the limits of its utility.

There are therefore two complementary issues to be considered in the appointment of CADD personnel: scientific and human relations. Inattention to either can prejudice a project group's work from the outset. It goes without saying that applying precisely the same criteria to other members of the triad (Fig. 1) will immediately raise the quality of interdisciplinary interaction. In

such an environment the existence of the less effective two-thirds categories can be gradually eliminated as project teams emerge as uniformly stronger agents of drug discovery.

IX. CONCLUSIONS

Assembly of talented computational scientists and the supporting software and/or hardware resources in pharmaceutical research centers is an industry-wide accomplishment. The latter introductory era has been followed by tentative movement from CADD as a support function to a collaborative partner. In some quarters CADD scientists have gained vital experience in the techniques of imaginative and utilitarian molecular design as well as in the politics of reducing concept to practice. On the whole, however, the integration of computer-assisted drug design methodology is in a transitional phase. The partners symbolized in Fig. 1 have yet to be consolidated such that the full creative potential of CADD thinking is expressed routinely in the properties of lead candidates. Problems that need careful attention include CADD placement in the research organization, mechanisms for credit distribution, correlated aspects of compound synthesis and molecular design, the selection and training of new-hires, and management sensitivity to the delicate interplay between science-in-action and human relations. When these and related issues are resolved within individual multidisciplinary research institutions, the power of CADD technology will begin to match its early but largely unfulfilled promise.

ACKNOWLEDGMENTS

I am grateful to Dr. Horace Brown and Dr. Peter Gund of Merck Sharp and Dohme for complete freedom to explore project team research boundaries in the transition from academia to industry. Dr. P. H. Jones of Searle provided deep-rooted support in subsequent consolidating steps required for developing a target-oriented CADD philosophy. Dr. J. Joseph Marr (Searle) afforded essential encouragement with the opportunity to establish one organizational variant of the Fig. 1 triad. Professor Lester Mitscher (U. Kansas) offered wisdom and inspiration at many critical moments. Finally, a special debt of appreciation is owed to members of the Searle Drug Design group, who have assisted without reservation the formulation of these thoughts, persisted when both hardware and human interfaces crashed, and practiced exquisitely the artful science of molecular design.

REFERENCES

1. W. J. Hehre, L. Radom, P. v. R. Schleyer, and J. A. Pople, *Ab Initio Molecular Orbital Theory* (Wiley, New York, 1986).
2. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.* **107,** 3902–3909 (1985).
3. J. J. P. Stewart, *J. Comp.-Aided Molec. Des.* **4,** 1–103 (1990).
4. N. L. Allinger, Y. H. Yuh, and J.-H. Lii, *J. Am. Chem. Soc.* **111,** 8551-8566 (1989).
5. S. J. Weiner, P. L. Kollman, D. A. Case, U. C. Singh, C. Ghio, G. Alagona, S. Profeta, Jr., and P. Weiner, *J. Am. Chem. Soc.* **106,** 765–784 (1984).
6. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, and W. C. Still, *J. Comp. Chem.* **11,** 440–467 (1990).
7. B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, and M. Karplus, *J. Comp. Chem.***4,** 187–217 (1983).
8. M. L. Connolly, *Science* **221,** 709–713 (1983).
9. For example, suites of programs have been combined and developed as comprehensive commercial modeling packages: SYBYL (Tripos Associates, St. Louis, MO), CHARMM

(Polygen Corp., Waltham, MA), DISCOVER (Biosym Technologies, Inc., San Diego, CA), BIOGRAF (BioDesign, Sunnyside, CA), PCMODEL (Serena Software, Bloomington, IA).
10. N. C. Cohen, J. M. Blaney, C. Humblet, P. Gund, and D. C. Barry, *J. Med. Chem.* **33,** 883–894 (1990).
11. T. J. O'Donnell, in *Computer-Aided Drug Design,* edited by T. C. Perun and C. L. Propst (Marcel Dekker, New York, 1989), pp. 19–54.
12. P. Gund, T. A. Halgren, and G. M. Smith, *Ann. Rep. Med. Chem.* **22,** 269–279 (1987).
13. T. K. Sawyer, *et al., J. Med. Chem.* **31,** 18–30 (1988).
14. R. H. Bradbury, J. S. Major, A. A. Oldham, J. E. Rivett, D. A. Roberts, A. M. Slater, D. Timms, and D. Waterson, *J. Med. Chem.* **33,** 2335–2342 (1990).
15. K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama, T. Ishida, and Y. Kiso, *J. Med. Chem.* **33,** 2707–2714 (1990).
16. *Computer-Aided Drug Design, Methods and Applications,* edited by T. J. Perun, and C. L. Propst (Marcel Dekker, New York, 1989).
17. R. P. Sheridan and R. Venkataraghavan, *Acc. Chem. Res.* **20,** 322–329 (1987).
18. R. P. Sheridan and R. Vankataraghavan, *J. Comp.-Aided Molec. Des.* **1,** 243–256 (1987).
19. M. F. Hibert, M. W. Gittos, D. N. Middlemiss, A. K. Mir, and J. R. Fozard, *J. Med. Chem.* **31,** 1087–1093 (1988).
20. M. S. Allen *et al., J. Med. Chem.* **33,** 2343–2357 (1990).
21. Y. C. Martin, *Tet. Comp. Method.* **3,** 15–25 (1990).
22. The University of California at San Francisco, Harvard, The University of Houston, and Washington University, St. Louis are notable exceptions. One-semester graduate courses in computational chemistry and molecular design are found at a number of other academic institutions. A Ph.D. degree program in computational methods is under consideration at the University of Georgia. A visionary but compacted alternative available to a wider audience is a week-long Residential School on Medicinal Chemistry held annually at Drew University.
23. From an informal survey of eight major pharmaceutical firms; Peter Gund and Thomas Halgren (Merck, Rahway), private communication, February 1987.
24. B. Odell, *J. Comp.-Aided Molec. Des.* **2,** 191–216 (1988).
25. J. A. Sikorski, K. S. Anderson, D. G. Cleary, M. J. Miller, P. D. Pansegrau, J. E. Ream. R. D. Sammons, and K. A. Johnson, in *Chemical Aspects of Enzyme Biotechnology: Fundamentals,* edited by T. O. Baldwin, F. M. Raushel, and A. I. Scott (Plenum, New York, 1990), pp. 23–39.
26. Observations are based in part on conversations with heads and members of drug-industry CADD units both in the U.S. and Europe over the past four years representating input from 15–20 different companies.
27. T. Ooi, M. Oobatake, G. Nemethy, and H. A. Scheraga, *Proc. Natl. Acad. Sci. USA* **84,** 3086–3090 (1987).
28. Y. K. Kang, G. Nemethy, and H. A. Scheraga, *J. Phys. Chem.* **91,** 4118–4120 (1987).
29. W. C. Still, A. Tempczyk, R. C. Hawley, and T. Hendrickson, *J. Am. Chem. Soc.* **112,** 6127–6129 (1990).
30. P. J. Hannan, R. Roy, and J. F. Christman, *Chemtech* **18,** 80–83 (1988).
31. G. B. Kauffman, *Today's Chemist* **2,** 13–15 (1989).
32. At Searle, computational excursions of this type are generally held to a minimum, since limited resources are most profitably focused on long-term collaborative efforts.
33. P. Gund, J. D. Andose, J. B. Rhodes, and G. M. Smith, *Science* **208,** 1425–1431 (1980).
34. J. G. Vintner, A. Davis, and M. R. Saunders, *J. Comp.-Aided Molec. Des.* **1,** 31–51 (1987).
35. K. F. Koehler, D. P. Spangler, and J. P. Snyder, *Abstracts of Papers,* 196th National Meeting of the American Chemical Society, Los Angeles, CA; American Chemical Society, Washington, DC, 1988, COMP 35; J. P. Snyder, K. F. Koehler, and D. P. Spangler, *Chem. Des. Auto. News* **4,** 1, 18–20 (1989).
36. J. H. Van Drie, D. Weininger, and Y. C. Martin, *J. Comp.-Aided Mol. Des.* **3,** 225–251 (1989).
37. R. P. Sheridan, R. Nilakantan, S. J. Dixon, and R. Venkataraghavan, *J. Med. Chem.* **29,** 899–906 (1986).
38. T. R. Hagadone, and M. S. Lajiness, *Tet. Comp. Method.* **1,** 219–230 (1988).
39. R. L. DesJarlais, R. P. Sheridan, G. L. Seibel, J. S. Dixon, I. D. Kuntz, and R. Venkataraghavan, *J. Med. Chem.* **31,** 722–729 (1988).
40. J. M. Blaney, and G. M. Crippen, *Quantum Chemistry Program Exchange,* Indiana University, Bloomington, IN, 1990 (DGEOM).
41. T. Joseph and A. Vedani, unpublished.

42. *Scientif. Am.* **259,** No. 4, October (1988).
43. M. A. Navia, P. M. D. Fitzgerald, B. M. McKeever, C.-T. Leu, J. C. Heimback, W. K. Herber, I. S. Sigal, P. L. Darke, and J. P. Springer, *Nature (London)* **337,** 615–620 (1989).
44. A. Wlodawer, M. Miller, M. Jaskolski, B. K. Sathyanarayana, E. Baldwin, I. T. Weber, L. M. Selk, L. Clawson, J. Schneider, and S. B. H. Kent, *Science* **245,** 616–621 (1989).
45. E. D. Thorsett *et al.*, *J. Med. Chem.* **29,** 251–260 (1986).
46. R. A. Dammkoehler, S. F. Karasek, E. F. B. Shands, and G. R. Marshall, *J. Comp.-Aided Mol. Des.* **3,** 3–21 (1989).
47. J. Greer, *Proteins* **7,** 317–334 (1990).
48. R. Rechid, M. Vingron, and P. Argos, *CABIOS,* **5,** 107–113 (1989).
49. M. Vingron, and P. Argos, *CABIOS,* **5,** 115–121 (1989).
50. T. Aoyama, Y. Suzuki, and H. Ichikawa, *J. Med. Chem.* **33,** 905–908 (1990).
51. For example, the package HOMOLOGY is currently being offered by Biosym Technologies, Inc.; San Diego, CA.
52. A. Brunger, *X-Plor Manual* (Yale University Press, New Haven, 1988).
53. P. A. Kollman, K. M. Merz, *Acc. Chem. Res.* **23,** 246–252 (1990).
54. J. Schneider, and S. B. Kent, *Cell* **54,** 363–368 (1988).
55. W. G. Farmerie, D. D. Loeb, N. C. Casavant, C. A. Hutchinson III, M. H. Edgell, and R. Swanstrom, *Science* **236,** 305–308 (1987).
56. C. Z. Giam, and I. Boros, *J. Biol. Chem.* **263,** 14 617–14 620 (1988).
57. J. E. Strickler, J. Gorniak, B. Dayton, T. Meek, M. Moore, V. Magaard, J. Malinkowski, and C. Debouck, *Proteins: Struc. Funct. Genet.* **6,** 139–154 (1989).
58. M. Miller, J. Schneider, B. K. Sathyanarayana, M. V. Toth, G. R. Marshall, L. Clawson, L. Selk, S. B. H. Kent, and A. Wlodawer, *Science* **246,** 1149–1152 (1989).
59. A. L. Swain, M. M. Miller, J. Green, D. H. Rich, J. Schneider, S. B. Kent, and A. Wlodawer, *Proc. Natl. Acad. Sci. USA* **87,** 8805–8809 (1990).
60. G. B. Dreyer *et al.*, *Proc. Natl. Acad. Sci. USA* **86,** 9752–9756 (1989).
61. T. D. Meek *et al.*, *Nature* **343,** 90–92 (1990).
62. T. J. McQuade, A. G. Tomasselli, L. Liu, V. Karacostas, B. Moss, T. K. Sawyer, R. L. Henrikson, and W. G. Tarpley, *Science* **247,** 454–456 (1990).
63. N. A. Roberts *et al.*, *Science* **248,** 358–361 (1990).
64. J. Erickson *et al.*, *Science* **249,** 527–533 (1990).
65. R. L. DesJarlais, G. L. Seibel, I. D. Kuntz, P. S. Furth, J. C. Alvarez, P. Ortiz De Montellano, D. L. DeCamp, L. M. Babe, and C. S. Craik, *Proc. Natl. Acad. Sci. USA* **87,** 6644–6648 (1990).
66. D. K. Berg and S. W. Halvorsen, *Nature* **334,** 384–385 (1988).
67. L. J. Emorine, S. Marullo, M.-M. Briend-Sutren, G. Patey, K. Tate, C. Delavier-Klutchko, and A. D. Strosberg, *Science* **245,** 1118–1121 (1989).
68. J. Deisenhofer and H. Michel, *Angew. Chem. Int. Ed.* **28,** 829–847 (1989).
69. R. Huber, *Angew. Chem. Int. Ed.* **28,** 848–869 (1989).
70. B. A. Wallace, and K. Ravikumar, *Science* **241,** 182–187 (1988).
71. D. A. Langs, *Science* **241,** 188–191 (1988).
72. This rough categorization stems from the exchanges cited in Ref. 26.