Collaborations

Academic Scientists and the Pharmaceutical Industry. Cooperative Research in Twentieth-Century America. JOHN P. SWANN. Johns Hopkins University Press, Baltimore, 1988. xiv, 249 pp., illus. $32.50.

Links between universities and industry in the conduct of biomedical research have been well established in recent years, and although their advantages and dangers are much discussed, the history of such relationships has been little investigated. Cooperative biomedical research between universities and the pharmaceutical industry developed in the 1920s and 1930s in the United States, and in this book Swann has selected the most important of these interactions for analysis, delineating how and why collaboration developed, the extent to which the intellectual, technical, and economic needs of the two parties created problems as well as mutual benefits, and the significant results of the collaboration, which included the development of important hormones, anticonvulsants, sedatives, and chemotherapeutic agents. Based largely upon manuscript collections of pharmaceutical companies and papers of academic scientists who pioneered in establishing ties with industry, Swann's case studies inform these themes while contributing to an understanding of the growth of pharmacology in America between the two world wars.

During the 1920s and 1930s pharmaceutical companies engaged what Swann calls general consultants, who had broad impact on programs of research, and specialist-consultants, who had narrower influence. Roger Adams, a distinguished organic chemist at the University of Illinois, served as a general consultant to Abbott Laboratories from 1917 to the late 1960s. In the same role, Alfred Newton Richards, a professor of pharmacology at the University of Pennsylvania, consulted with Merck and Company from 1930 to 1959. Adams and Richards helped to develop company in-house research programs, served as liaisons with the academic community, fostered close relationships between their universities and the companies, and kept the companies current on research in related fields. Richards was a particularly strong influence on the direction of Merck's research and played an important role in the transformation of Merck into a research-oriented firm. Swann provides rich details of the interactions of academic scientists with pharmaceutical companies, conveying a sense of what the consultantships meant to both parties, financially and professionally.

Specialist-consultants influenced pharmaceutical research in more specific ways. Firms often relied upon specialists' expertise to overcome particular deficiencies in their own research staffs and to take advantage of fast-breaking developments. For academic scientists these consultantships were sources of graduate fellowships and research support. Moreover, royalties from the sale of drugs provided money for individual scientists and university laboratories for years in those cases where provision was made for them. As examples of this type of relationship Swann examines the microbiologist Selman Waksman's consultantship with Merck on antibiotics and industrial fermentations, the pharmacologist Chauncey Leake's investigation of arsenicals for Parke-Davis and Company, and the medicinal chemist Lyndon Small's work on the preparation of morphine derivatives for Merck, E. R. Squibb and Sons, and Mallinckrodt. All three cases illustrate the many benefits to the scientists (raw materials, technical advice, and funds for their research) and the growing awareness that firms had to maintain contact with outside experts in fields that held promise for the development of new drugs.

Swann also deals with collaboration aimed at developing specific therapeutic agents following their initial discovery. The examples given are ones that had great effects upon public health and the parties involved. They also illuminate the disagreements that arose because of differing priorities and interests. The collaboration between researchers at the University of Toronto and Eli Lilly and Company in 1922 and 1923 for the development of insulin is well known. It transformed Lilly into a major drug firm and provided the university with scientific recognition and about $8 million in royalities from patents. Despite the overall success of the project, confrontations developed as the two sides struggled to appreciate each other's objectives. The chief issue of contention was Lilly's wish to monopolize or at least have a commercial advantage with respect to insulin. Less well known is Lilly's work with two university medical schools to develop commercial extracts from liver. In 1927–1928 Lilly researchers collaborated with scientists at Harvard University to produce an extract useful against pernicious anemia. Following this, Lilly arranged for the University of Rochester to conduct clinical evaluations of various fractions for activity against secondary anemia. This collaboration did not lead to confrontations over the issue of monopolization as had the insulin collaboration, chiefly because Harvard and Rochester preferred informal arrangements rather than contractual agreements.

Today, as universities and industries are eager to develop research contracts on a wide scale, we need to reflect on the issues that arise in such relationships. Swann has identified many of these and documented them carefully, and his book presents them in clear historical perspective.

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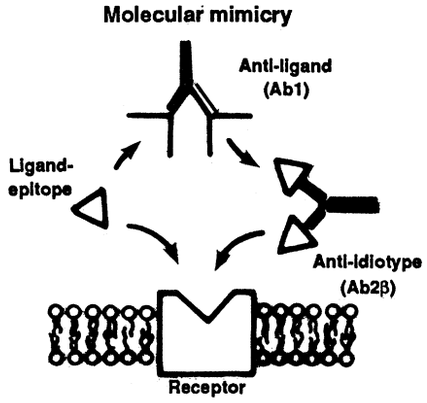
Immunological Networks

Anti-Idiotypes, Receptors, and Molecular Mimicry. D. SCOTT LINTHICUM and NADIR R. FARID, Eds. Springer-Verlag, New York, 1988. xii, 322 pp., illus. $65. From a symposium, Quebec, Canada, June 1986.

The elaboration of the idiotype network theory 15 years ago by Niels Jerne created a context for the examination of a singular and remarkable feature of the immune system: namely, that its receptors and specific secreted products, or antibodies, not only recognize the external world of antigenic determinants (epitopes) but also recognize antigenic determinants on the immune receptors themselves (idiotopes). Ten years earlier, in 1963, J. Oudin's and H. G. Kunkel's groups had identified the set of such idiotopes on single immunoglobulin molecules as the *idiotype*, which, it is now realized, represents unique idiotopes as well as those shared with antibodies of related or unrelated specificity for antigen. Jerne characterized the immune system as a web of immunoglobulin variable-region domains, a concept that when taken to its extreme might embrace all immune receptors in the organism.

Jerne's network theory also included the corollary that within the reflective symmetries of idiotopes (Ab1), anti-idiotopes (Ab2), and anti-anti-idiotopes (Ab3, and so forth) formed within the organism's immune system would be found representatives (internal images) of most or all of the epitopes of the external universe. In fact, as a



Working model of anti-idiotype mimicry. In this model anti-ligand antibody (Ab1) is equivalent to receptor and anti-idiotype antibody (Ab2β) mimics the original ligand. [Adapted from *Anti-Idiotypes, Receptors, and Molecular Mimicry*]

direct extension of these ideas, Sege and Peterson discussed another level of internal imaging, pointing out that the binding sites of some specific antibodies (Ab1) to ligands such as hormones or drugs might sterically and immunologically resemble the binding sites on their physiological receptors. Accordingly, certain anti-idiotypes (termed Ab2β by Jerne) raised to ligand-binding sites on Ab1 should serve as agonists or antagonists of the physiological receptor, and binding to them should be inhibitable by the original ligand or drug.

This volume of 20 papers explores these essentially quadrilateral relationships among ligand-epitope, physiological receptor, Ab1, and Ab2β at many levels (see illustration). The receptors studied recognize peptides and hormones important in neurologic or cardiovascular function, lymphocyte regulatory molecules, cell growth factors, and neutralization sites on viral envelopes, among others. The common thread in the monograph is the exploration of molecular mimicry by sites on the rather bulky immunoglobulin molecules for the potpourri of generally smaller ligands that bind to a variety of physiological receptors.

Particularly interesting in this respect are the discussions and experiments related to more precisely defining the shape of internal images on the anti-idiotypic Ab2β molecules. While Ab2β and ligand-epitope will compete at the Ab1 receptor site for binding, exactly how similar is the image of Ab2β to that of the epitope, what can be inferred about the shape of the hypervariable determinant regions on Ab1, and what is the energy of interaction between Ab2β and Ab1, compared to that between epitope and Ab1? Glasel's article on opiate receptors is especially illuminating on these questions; it also considers the physical basis for agonist versus antagonist function in Ab2β. Linthicum's group examines several of these issues in its analysis of neuroleptic ligands and their internal images. (A flaw apparent in early chapters and propagated in later ones is lack of uniformity in the definition of idiotypic terms even for basic concepts such as "internal image," which some authors mistakenly define as a structure complementary to the epitope.)

One reason for the considerable interest in the type of biochemical mimicry performed by the immune system lies in exploitation of anti-receptor Ab2β molecules for isolation and study of receptors such as the β-adrenergic receptor that are expressed only in small amounts on the surface of cells. Several contributions (for example, Farid; Sawutz and Homcy; Osheroff) consider the interactions of idiotypic ligands with such receptors as a means for functional characterization of the hormone-receptor system.

At times, viruses can use an unrelated integral membrane receptor as a viral attachment site (for example, the use of the β-adrenergic receptor by reovirus, as described by Gaulton and Greene). The interactions of viral receptors with antigenic retroviruses can become intercalated into the affairs of the idiotypic lymphocyte network (Ardman and Burdette). Ab2β molecules, raised to antibodies specific for viral gp70 determinants in susceptible preleukemic strains, react with gp70-binding sites on leukemic or preleukemic cells, regulating their growth.

For a "pure" immunologist, the crossover of the idiotypic network with the universe of physiological receptors represents a broadening of an already complex system whose rules are still being learned. How heterogeneous are the idiotypic sites recognized by anti-idiotypic antibodies? (Quite.) How frequently do internal image Ab2 appear? (Not very.) Do Ab2 invariably result in the individual from the injection of antigen? (No.) How does the response to antigen compare to the response raised against internal image Ab2β? (A complex issue.) Such questions are raised in many papers, with respect to innocuous as well as potentially pathogenic antigen systems.

An area of great importance, especially in current planning for the use of idiotypic internal image vaccines, is the description of the T-cell epitope content of Ab2β molecules. T-cell collaboration is known to be necessary for B cells to mature to the stage of antibody formation, and other subpopulations of T cells may themselves effect the elimination of the enemy within (infectious agents, tumors, and so forth). In a global consideration of network theory, Cleveland masterfully addresses several broad issues relating to "T cell–stimulating internal images" and their coexistence with "B cell–stimulating internal images," extending this aspect of network theory considerably beyond previous treatments. Although the accelerated march of immunologic research has already rendered certain of Cleveland's concerns obsolete, this thoughtful paper raises many pertinent notions about life in the "society of lymphocytes."

As is evident throughout this interesting volume, members of lymphocyte society perforce must interact within the organism with parallel and diverse cellular populations, decorated with receptors of differing function. The first glimmerings of an appreciation of the immune system's accommodation to its neighbors from other systems can be gleaned from this monograph. It should be accessible not only to immunological sociologists but also to chemists and biologists who are fascinated by the passage of information in discrete systems and by interactions among systems usually considered as totally separate entities.

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Plant Interactions

Plant Strategies and the Dynamics and Structure of Plant Communities. DAVID TILMAN. Princeton University Press, Princeton, NJ, 1988. xii, 360 pp., illus. $45; paper, $15.95. Monographs in Population Biology, vol. 26.

The diversity of the earth's vegetation is striking and marvelous. We are in an era when much of plant ecology is dedicated to describing and explaining the diversity, the details that make the responses of each species in each habitat unique. David Tilman's new book goes in the opposite direction, with an attempt to identify and explain some of the functional processes that underlie broad patterns in the structure and dynamics of plant communities. These patterns include evolutionary convergence of vegetation in separate but similar climates and the consistency of vegetation succession on disturbed or bare sites.

Tilman begins from two assumptions. One is that a general theory must be mechanistic, based on quantifiable functional attributes. The second is that a general theory should, at this point, be simple and illustrative, rather than detailed and sophisticated.

Tilman's argument extends groundwork laid in his 1982 book *Resource Competition and Community Structure* (Princeton University Press), where he developed a conceptual-graphical model of competition for multiple