theoretical treatments or electronic analogs for biological pacemakers, supplanted by biologically relevant formal models anchored firmly by experimental data. Also evident is a manifold increase in physiological investigations aimed at identifying the cellular organization of pacemaking systems. Whereas the 1960 symposium contained a single paper on pacemaker localization within the nervous system, nearly one-third of the current volume is devoted to the physiological analysis of pacemaking systems. Similarly, other additions reveal that the field has profited from its newly acquired sophistication with genetic, endocrinological, and electrophysiological techniques.

A more careful reading reveals a source book that is impressively comprehensive, covering both behavioral and physiological aspects of circadian rhythms as well as related aspects of circannual, tidal, and lunar periodicities. Also covered is the involvement of circadian clocks in photoperiodism and time-compensated orientation.

Though the volume is clearly too extensive to have a single motif, one important idea stressed throughout is that most, if not all, endogenous timing systems consist of multiple oscillators. Certainly the notion of multiple oscillators within one organism is not new. As early as 1960 Pittendrigh concluded, "We are forced, in fact, to abandon our common current view that our problem is to isolate and analyze 'the endogenous rhythm' or 'the internal clock' and are faced with the conclusion that the organism comprises a population of quasi-autonomous oscillatory systems." What is new, however, and not implicit in Pittendrigh's dictum, is that the conceptually distinct oscillators are turning out, in many cases, to be anatomically distinct entities. This finding, more than any other, shapes our contemporary view about the organization of biological timing systems, sets boundaries on purely reductionist strategies, and makes it clear that a complete understanding of endogenous timing will require an appreciation of the integrative relationships among pacemakers.

While the multioscillator nature of biological timekeeping is a major theme, the book is balanced in its overall coverage and lives up to its designation as a comprehensive reference text. For example, it provides a most detailed treatment of the entrainment process, including entrainment theory (chapters 5, 6, and 7), identification of critical environmental signals (chapters 6 and 11), and localization of sensory structures mediating entrainment (chapters 9 and 13). In addition, as mentioned, there is outstanding coverage of photoperiodic phenomena both in insects (chapter 22) and in vertebrates (chapter 23) as well as excellent reviews on noncircadian endogenous periodicities.

Aschoff insisted that the 25 contributors use a common technical vocabulary, and this strategy significantly avoids the dialects that have sometimes plagued this field. Though there is unevenness in quality and some redundancy, most of the chapters are well written and a few truly elegant (for example, chapter 5 by Pittendrigh).

In summary, the volume should serve the biological community as an important reference source as well as a textbook.

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Risk Factors in Breast Cancer

Hormones and Breast Cancer. Papers from a conference, Oct. 1980. MALCOLM C. PIKE, PENTTI K. SIITERI, and CLIFFORD W. WELSCH, Eds. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1981. xii, 492 pp., illus. $65. Banbury Report 8.

How can hormonal function influence a woman's risk of breast cancer? The question is a major clinical and public health issue and also presents complex methodological problems in epidemiology, endocrinology, and tumor biology. As this volume of symposium proceedings reveals, some elements in this relationship have been quite clearly defined, but we know much less about the interaction of endogenous hormones with one another and with exogenous agents that may initiate or promote tumor growth and about the impact of these interactions on a woman's risk of breast cancer.

One perspective from which to approach the relationship of hormones to human breast cancer is that of the endocrinology of clinically asymptomatic women whose family histories of breast cancer statistically increase their risk of developing the disease. Probably the factor most dramatically increasing a woman's risk of breast cancer is the presence of breast or ovarian cancer in close relatives, especially if these relatives developed tumors bilaterally while young (*1*). In at least some such families, susceptibility to breast cancer appears to be inherited (*2*). But how might susceptibility genes be expressed biochemically and physiologically? Some fascinating clues appear in this volume.

Bulbrook *et al.* report that in a series of prospective studies they have demonstrated that healthy women in their 40's and 50's with close family histories of breast cancer have depressed thyroid function compared with women of the same ages without such family histories. Even more dramatic, women with a family history of breast cancer who later develop the disease have depressed thyroid activity compared with other breast cancer patients, years before any of them are diagnosed. Bulbrook *et al.* suggest that nonfamilial breast cancer may be unrelated to thyroid function, whereas familial breast cancer may be due to inherited thyroid abnormalities or other defects influencing thyroid function in some women.

Furthermore, Siiteri *et al.* report that they have determined that in some breast cancer patients the proportion of estrogen circulating freely in serum is higher than in unaffected women. This is important because only "free" estrogen appears to be available to target cells in the breast. Siiteri *et al.* attribute the elevation in the percentage of free estrogen to depressed levels of sex-hormone–binding globulin (SHBG) in serum and suggest that inherited low SHBG activity or defective SHBG may be responsible for familial susceptibility to breast cancer. A related study reported by Ottman *et al.* of the characteristics of estrogen receptors in the tumors of familial and nonfamilial breast cancer patients supports this hypothesis. The two groups of patients do not differ in amount of estrogen receptor, but the dissociation constants (K_D) of the receptors in familial patients' tumors are significantly higher than those of nonfamilial patients. Ottman *et al.* suggest that this difference may result from higher levels of estrogen in breast tissue of some familial patients. Because thyroid hormones stimulate SHBG, the results reported by Siiteri's and Ottman's groups may represent a later step in the same process Bulbrook *et al.* describe.

A third series of studies, of totally different design, are analyses by Henderson and Pike of plasma levels of estrone plus estradiol ($E_1 + E_2$) and of prolactin in the healthy daughters of unselected breast cancer patients, daughters of bilateral, premenopausal breast cancer patients, and daughters of unaffected women. Their results support the notion that

elevated $E_1 + E_2$ and prolactin secretion (stimulated by estrogen) are associated with high risk due to family history of breast cancer, particularly of bilateral, premenopausal disease.

This hormonal cluster—depressed thyroid function, low SHBG activity, elevated free estrogen, and elevated prolactin—that may be associated with inherited susceptibility to breast cancer suggests new hormonal-epidemiological studies. For example, Korenman hypothesizes that the duration of periods of estrogen excess, or unopposed estrogen, in a woman's life determines her risk of breast cancer and that conditions such as nonovulatory cycles after menarche, short–luteal-phase cycles, and long–follicular-phase cycles are associated with estrogen excess. He proposes that these conditions, which may occur in cycles of normal total length, be analyzed in young women whose family history puts them at high risk. This is particularly important given the discovery that progesterone deficiency increases subsequent risk of breast cancer (*3*).

Unfortunately, none of the authors reports the effect exogenous estrogens may have on women already at familial high risk of breast cancer. Kelsey, in her otherwise thorough and critical review of epidemiological studies of oral contraceptives, menopausal estrogens, and risk of breast cancer, omits the possibly substantial synergistic effect of inherited susceptibility. By analyzing study subjects at high familial risk separately from other subjects, some of the ambiguity in the published results might be resolved.

A complexity accompanying any analysis of hormonal (or other) possible mechanisms for inherited susceptibility to breast cancer is that even in those families in which susceptibility is most strongly influenced by genetic factors only 50 percent of the daughters of breast cancer patients are, on average, at high risk (*1, 2*). Unfortunately, the high-risk and normal-risk women in such a sample cannot generally be distinguished from one another; such distinctions are one goal of the hormonal analysis. However, as long as statistical analysis is limited to comparisons of mean values of women from high-risk families with mean values of women from normal-risk families, true differences characteristic of the high-risk subset of women may be obscured. More appropriate would be analyses of bimodality in hormone levels within the "high-risk" sample, indicating risk heterogeneity. A simple inspection of Henderson and Pike's $E_1 + E_2$ and prolactin results (p. 117) indicates that perhaps one-third of the daughters of breast cancer patients not selected for bilateral tumors or young age at diagnosis had elevated plasma hormones. Would a larger proportion of the daughters of bilateral, premenopausal patients have elevated levels of $E_1 + E_2$, prolactin, or both?

Integrated endocrinological-epidemiological studies can elucidate still more of the relationship between hormones and breast cancer. One potentially very productive approach would be the concurrent analysis of thyroid function, percentage of free estrogen, length of luteal and follicular phases of cycles, and prolactin level in one group of healthy women from families with high incidence of breast cancer, by means of statistical techniques that do not obscure the heterogeneity of risk within such a population.

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Protein Evolution

The Evolution of Protein Structure and Function. A Symposium in Honor of Professor Emil L. Smith. Los Angeles, June 1979. DAVID S. SIGMAN and MARY A. B. BRAZIER, Eds. Academic Press, New York, 1980. xviii, 350 pp., illus. $25. UCLA Forum in Medical Sciences, No. 21.

Emil L. Smith has long been a towering figure among biochemists. His influence has been felt in a variety of ways, not the least of which is his co-authorship of a long-running and successful textbook. But it is his work on the structure and evolution of proteins that has earned him his enormous reputation. The number of proteins he has worked on is overwhelming: leucine aminopeptidase, papain, subtilisin, cytochrome *c*, histones, and glutamate dehydrogenase, to name the most important. His interest in proteins began more than 40 years ago, at which time biochemical emphasis was on directly relating structure and function. With the introduction of amino acid sequencing techniques in the 1950's, much attention was shifted to the evolution of proteins as a feature relating structure and function. Smith and his colleagues helped pioneer this movement, especially with their studies of cytochrome *c*.

This collection of essays in honor of Smith is divided into sections dealing with enzymology, protein structure and function, and evolution, but the theme of evolution of structure and function runs throughout. Some of the most enjoyable chapters intertwine some personal history with a review of a subject. The opening chapter, by Stanford Moore, is a charming memoir of how he and Smith began studies of proteins with Max Bergmann at the Rockefeller Institute, after Smith had finished his Ph.D. with Selig Hecht at New York University. Moore deftly captures the spirit of the times and the technological developments that were required for progress in understanding the chemistry of proteins and how these influenced the choice of problems. James Bonner also manages to intercalate a good deal of reminiscing when chronicling the birth of chemical studies of chromosomal proteins. These two chapters alone would make the book worth owning for any protein chemist with a sense of history.

But the fact is that all the chapters are interesting. There is a cluster of chapters on bacterial enzymes, including one on *recA* protein by I. Robert Lehman, another on in vitro enzyme evolution studies by Brian S. Hartley, and a splendid one on virtually every structural feature of β-galactosidase by Irving Zabin. From that point on the titles are mostly up-to-date echoes and reminders of subjects that Smith himself worked on: metalloenzymes (Bo G. Malmström), glycoprotein hormones (John G. Pierce and Thomas F. Parsons), histones (R. J. De Lange), and cytochrome *c* (E. Margoliash). The authors seem to have made distinct efforts to keep their contributions novel, not simply to reprint previously published material. Other chapters include an insightful approach to analyzing those aspects of protein structure that lead to thermal stability (Patrick Argos *et al.*) and a reiteration of the neutral mutation concept (Thomas H. Jukes). Richard E. Dickerson persuasively makes the case that we have all descended from a defective photosynthetic bacterium.

By and large this is a very enjoyable compendium. All protein chemists will want to own it for its reflection of an age, and all biochemists can read it with profit