Living history: F. Eugene Yates

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FRANCIS EUGENE YATES (Fig. 1) was born on February 26, 1927, in Pasadena, CA. He has been a member of the American Physiological Society (APS) for >50 yr. He is in his 82nd year of age and is still active in scientific work. His career includes experimental, clinical, and theoretical studies in the following areas:

- Congestive heart failure (CHF)
- The hypothalamic-pituitary-adrenocortical feedback system
- Computer modeling of endocrine and metabolic systems
- Systems biology, especially with regard to self-organizing systems
- Aging: Why do we grow old and die, and how fast?
- The temporal organization of living systems: circadian and ultradian rhythms
- Updating Cannon’s “homeostasis” as a new physical biology for physiology that he calls “homeodynamics: a physical heuristic for life and the sciences of complexity”
- Space biology [humans to Mars National Aeronautics and Space Administration (NASA) program for the National Space Biomedical Research Institute]
- The controlled delivery of therapeutic agents (with the ALZA Corporation)
- Alzheimer’s disease (for the John Douglas French Alzheimer’s Foundation)

He is a founding member of the Biomedical Engineering Society (BMES) and has served as its president.

He has been a member of Publications Committees of three societies: APS, the Endocrine Society, and BMES, and Chairman of two of them.

He has founded a new journal for each of those societies:

- American Journal of Physiology-Regulatory, Integrative and Comparative Physiology for APS
- Annals of Biomedical Engineering for BMES
- Endocrine Reviews for the Endocrine Society. (This journal currently has the highest “impact factor” of any endocrine journal.)

In addition, he has served as Editor-in-Chief of each of the first two journals for 7 yr.

Along the way, he organized three major international conferences:

- Self-Organizing Systems (1979, Ripple Foundation, American Institute of Biological Sciences, and National Academy of Sciences of Yugoslavia)
- Nonlinearities in Brain Function (1982, Kroc Foundation)
- Chemically Based Computer Designs [1983, National Science Foundation (NSF)]

He has been on the faculties of four universities: Harvard University (Physiology Department), Stanford University (Physiology Department), University of Southern California (USC; Biomedical Engineering Department), and University of California-Los Angeles (UCLA; Department of Medicine and Department of Chemical Engineering), where he held the Ralph and Marjorie Crump endowed Professorship of Medical Engineering.

The Harvard Years (1953–1960)

Personnel who made substantial and sustained contributions to the scientific activities of the Yates laboratory or programs during the Harvard years are shown in Table 1.

In July 1953, Yates completed 2 yr of active duty as a physician for the United States Navy during the Korean War, and, in September 1953, he joined the Department of Physiology at Harvard Medical School, where a Webster-Underhill fellowship awaited him. Yates was assigned to work in the laboratory of A. Clifford Barger. Barger had recently developed an experimental approach to CHF and wanted two postdoctoral researchers to join him. The other was Abraham Rudolph. The three worked for the next 2 yr, assisted by the technician Franklin Smith, to study the changes in renal circulatory dynamics [glomerular filtration rate (GFR) and renal blood flow (RBF)] occurring in trained, conscious, resting dogs in three clinical stages: 1) normal (control), 2) after surgically induced tricuspid valve insufficiency (to elevate central venous pressure), and 3) after added pulmonary artery stenosis. By the third stage, the dogs developed ascites and other signs of CHF.

In 1953, there were two theories about salt and water retention characteristic of CHF: 1) the “forward” theory, which stated that fluid retention developed because the kidney was not adequately perfused from its arterial supply as cardiac output fell; and 2) the “backward” theory, which stated that it was venous congestion of the kidney that interfered with renal filtration and blood flow. The aim of Barger’s studies was to define, as precisely as renal clearance methods would allow, just what did happen to renal hemodynamics as cardiac performance was diminished in a graded fashion. (It was already widely suspected that some unknown salt-retaining factor was also involved. Aldosterone was just then being discovered as a...
mineralocorticoid but was not yet widely available for physiological studies.) Pressing renal clearance methods and flame photometric analyses (for sodium and potassium in plasma and urine) to their limit, the team carefully mapped the pattern of decreases in GFR, RBF, filtration fraction, and osmolalities as CHF developed (1). The study was successful in clearly defining the progressive decreases in renal hemodynamics, but clearance methods were too coarse to detect subtle causalities for the sodium and water retentions.

At the end of his fellowship, Dr. Yates had planned to accept a proffered residency in internal medicine across the street at the P. B. Brigham Hospital, but when he was also offered a faculty position in the Department of Physiology, he realized that this basic science was his real interest, and he choose that course—a decision he has never regretted. In setting up his physiology laboratory, Yates wanted to continue his study of CHF, and he chose the “backward” failure perspective, in which venous congestion was a key feature. He developed a venous congested rat model by surgically creating partially graded constriction of the hepatic veins. This constriction did not elevate venous pressure at the kidney or alter RBF. Yates predicted that congestion of the liver would alter the hepatic inactivation of corticosteroids including, of course, aldosterone. The first step inactivators were Δ4-steroid hydrogenases (Δ4SH), which used reduced triphosphopyridine nucleotide (TPNH (older nomenclature of those days; now NADPH)) as a cofactor. It seemed likely that the enzymes might be affected by lowered oxygen pressures within the congested liver, impairing corticosteroid inactivation. After the chronic liver congestion was well established (later confirmed histologically) and a linear assay for the enzymes was validated, liver homogenates were killed at the end, and he offered his surplus female animals.

As soon as the livers of normal female rats were assayed, it was found that they had three or more times the Δ4SH activity of males per milligram of liver (50) and, furthermore, that their adrenals were much larger than those of males. These differences were later found to be associated with much faster clearances by females of plasma corticosterone in vivo (7). That unexpected finding led to a detailed study of these hepatic enzymes as they influence the adrenocortical feedback system.

The adrenal cortex and hepatic Δ4SH. Prof. Yates and his Harvard group next launched a series of studies on experimental means to change hepatic Δ4SH activities by means of thyroid hormones and dietary alterations (9, 61). When all the data were collected together, including the natural sex difference, the set consisted of a 10-fold range of hepatic enzymatic activities. Their hypothesis was that as the activity of Δ4SH was independently increased, the plasma levels of corticosterone (the main corticosteroid of the rat) would be dependently dragged down, and, therefore, the corticosteroid inhibition of ACTH secretion via negative feedback would be decreased, ACTH secretion would be increased, and adrenal enlargement would result. Adrenal weights should be positively correlated with the hepatic Δ4SH activity. A novel plot of the total hepatic Δ4SH capacity (abscissa) versus total adrenal weight (ordinate) was surprisingly linear, with a steep positive slope and little scatter, over an order of magnitude range on the abscissa (61). (The positive, small intercept on the ordinate was the expected weight of the adrenal medulla.) This graph is dramatically shown in Fig. 2. To Yates, that plot invited applications of formal engineering feedback principles to endocrine feedback systems and introduced the concept that the liver had a special influence on the adrenocortical system (21).

The further tests of the hypothesis led to Yates’s group’s receiving the first Upjohn Award of the Endocrine Society. Yates was then invited by an editor of Physiological Reviews (Eugene Landis) to prepare a comprehensive review article from a feedback regulation and control perspective (59).

The Stanford Years (1960–1970)

People who made substantial and sustained contributions to the scientific activities of Yates’ laboratory or programs during the Stanford years are shown in Table 1.

In 1960, Yates returned to Stanford University as its opened its modernized medical school in Palo Alto, CA. Immediately, he began to develop formal computer models of aspects of the adrenocortical system (22, 49). The National Institutes of Health (NIH) at this time was interested in developing research and teaching in the new field called biomedical engineering, and Yates became an early member of the relevant NIH study sections.

One of the elementary concepts in elementary control engineering was that of proportional-derivative control as a means to speed up responses to disturbances, by anticipating the future. Yates thought that the stress-responsive adrenocortical negative feedback system might have both rate sensitivity (derivative signal) and level sensitivity (proportional signal). With his Stanford graduate student Mary Dallman, he devised a protocol to test that idea, and the results confirmed the hypothesis (Fig. 3) (5).

In the late 1950s, interest in the hypothalamic factor governing ACTH release from the anterior pituitary began to become intense. The factor, corticotropin-releasing hormone (CRH), was eventually identified by Wylie Vale. Purified CRH was not yet available for general use, but it was possible to prepare hypothalamic extracts with that activity, called corticotropin-releasing factor (CRF) (6). Graduate student Sharon...
Russell established an assay exploiting stereotaxic microinjections into the pituitaries of rats in the Yates laboratory (6). Using that preparation, it was possible to answer an old question: Is the negative feedback action of corticosteroids detectable at the pituitary level? (It was already thought to be effective at a hypothalamic level.) The answer was “yes” (17).

The same technique answered another important question: How does vasopressin provoke ACTH release (8)? They found that the chief way it did so was by potentiating the action of CRF (58). (Up to that time, it had been erroneously believed that vasopressin was CRH.)

Multiplexing in adrenocortical signaling. Another idea from Yates’ Stanford group was that the protein binding of corticosteroids by albumin and transcortin (13), universally thought to

Table 1. People who made substantial and sustained contributions to the scientific activities of Yates’ laboratory or programs

<table>
<thead>
<tr>
<th>Individual</th>
<th>Position</th>
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<tr>
<td>The Harvard years (1953–1960)</td>
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<tr>
<td>John Urquhart</td>
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<td>Arthur Herbst</td>
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<td>Kathleen Mao</td>
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<td>Mary Fenner</td>
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<td>David Glenister</td>
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<td>Ernst Knobf</td>
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<td>The Stanford years (1960–1969)</td>
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<td>Ingrid Richardson</td>
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<td>Sharon Russell</td>
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<td>Janice Maran</td>
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<td>Mary (née Fenner) Dallman</td>
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<td>Ralph Miller</td>
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<td>Angel Gonzales Luque</td>
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<td>Manfred L’Age</td>
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<td>Bobby Haller</td>
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<td>Kenneth Diamond</td>
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<td>Lorreta Barker</td>
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<td>Margaret Mahoney</td>
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<td>Nancy Keller</td>
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<td>Lee Sendelbeck</td>
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<td>Fred Burbank</td>
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<td>Bob Marcus</td>
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<td>Margaret Yates</td>
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<td>John Urquhart</td>
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<td>George Hedge</td>
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<td>A. P. S. Dharawal</td>
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<td>Atsuo Kawai</td>
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<td>Bob Brennan</td>
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<td>William Halpern</td>
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<td>The USC years (1969–1980)*</td>
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<td>Michael Gold</td>
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<td>Bob Cohen</td>
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<td>George Meier</td>
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<td>Robert Odell</td>
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<td>Ed Kulis</td>
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<td>Donald Marsh</td>
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<td>Richard Bergman</td>
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<td>Janice Maran</td>
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<td>Laurel Benton</td>
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<td>Philip Anderson</td>
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<td>John Urquhart</td>
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<td>Stuart Smith</td>
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<td>The UCLA years (1980–2004)†</td>
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<td>Steve Berry</td>
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<td>Peter Kugler</td>
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<td>Donald Walter</td>
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<td>Timothy Poston</td>
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<td>Alan Garfinkel</td>
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<td>Arthur Iberall</td>
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<td>Harry Soodak</td>
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<td>Laurel Benton</td>
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<td>Jennifer Parker</td>
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<td>Bada Drakulic</td>
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<td>Simon Gister</td>
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<td>Rene Thom</td>
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<td>Ralph Abraham</td>
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<td>Monique Mere</td>
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<td>Bob Cohen</td>
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<td>Ed Deland</td>
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GS, graduate student; T, technician; SS, senior collaborators, consultants from other departments or institutions, or independent; PD, post-doctoral fellow; VS, visiting scholar; A, administrative assistant; MP, mini-pump group. *In 1977, Prof. Yates became Director of the National Institutes of Health/University of Southern California (USC) Biomedical Engineering Center and had many faculty associates and other colleagues. Only those very close to his own laboratory interests are named here. †In 1980, Prof. Yates was appointed Director of the Crump Institute for Medical Engineering and had up to 40 people in his employ. Only those close to his personal research activities are listed here, along with some close consultants. ‡When Alejandro (Alex) Zaffaroni, in 1968, founded ALZA as the first pharmaceutical company devoted exclusively to unique formulations that precisely controlled the delivery of therapeutic agents, he looked for some physiologists with special interests in biological regulations and controls. Among them was Prof. Yates, who was appointed Consulting Principal Scientist in 1969. With the approval of his university (USC) and later the University of California-Los Angeles (UCLA), where he held several professorships (Medicine, Chemical Engineering, and Medical Engineering), Yates regularly spent 1 day/wk at ALZA’s campus in Palo Alto, CA, for the next 28 yr. He worked with many different project development teams and had close relationships with most of ALZA’s senior scientists. Only a few of his colleagues are listed here. All funds received from ALZA in support of Yates’ appointment were directed (at Yates’ request) to USC and UCLA as unrestricted gifts for research, not personal income. Some ALZA personnel with Yates had frequent or important associates are listed.

Russell established an assay exploiting stereotaxic microinjections into the pituitaries of rats in the Yates laboratory (6). Using that preparation, it was possible to answer an old question: Is the negative feedback action of corticosteroids detectable at the pituitary level? (It was already thought to be effective at a hypothalamic level.) The answer was “yes” (17).

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The hepatic inactivating enzymes (adrenal weight/100 g body wt) was linearly dependent on the activity of the injections, and thyroidectomy. The weight of the adrenal cortices (sum of some others) together in a comprehensive APS Maran, Yates brought all of his Stanford results (and those of became Director and NIH Principal Investigator of the new the USC years are shown in Table 1.

The USC Years (1970–1980)

People who made substantial and sustained contributions to the scientific activities of Yates’ laboratory or programs during the USC years are shown in Table 1.

In 1969, Dr. Yates accepted a position at USC, where he became Director and NIH Principal Investigator of the new Biomedical Engineering Center. With graduate student Janice Maran, Yates brought all of his Stanford results (and those of some others) together in a comprehensive APS Handbook chapter on the adrenal cortex (52). In the laboratory, now working with conscious, unrestrained, trained dogs, he and Maran went on to answer yet another question then important in the field: Can angiotensin II exert ACTH-releasing activity at the pituitary? The answer was “yes” (14). With postdoctoral fellow Ralph Miller and student George Meier, they also applied a linear, mean-squared estimator to data from their adrenocortical experiments and modeling to obtain a unique, quantitative characterization of adrenocortical function: the static gain and dynamics (15). Next, the estimate of the loop gain was confirmed by an elaborate and unique two-dog cross perfusion protocol developed with student Alan Lefcourt, which actually opened the feedback loop in a controlled manner for the first time. The open loop dimensionless gain (an engineering specification that is fundamental to assessing the potency of negative feedbacks) proved to have a value of 6.0, unusually high for an endocrine system. This surprising result was later exactly confirmed by repeating the experiments with a different team of assistants. Their results were detailed in a chapter Yates was invited to write for the textbook of Medical Physiology edited by Vernon Mountcastle (54). Soon after, Prof. Yates responded to an invitation to give a seminar from some members of the reproductive biology community who had noticed his computational approach to adrenocortical physiology and wanted a general version of the simulation programs for their own society’s interests. The published result of his lecture is Ref. 26.

Systems biology. By this time, Prof. Yates had an established reputation for a “systems biology” approach to physiology, including computer simulations. Yates was invited to supply an extensive chapter in a three-volume series entitled Biological Regulation and Development. That comprehensive chapter was entitled “Systems analysis of hormone action: principles and strategies” (28), and it extended ideas he had been developing at USC in the early 1970s (23, 24) regarding systems analysis as applied especially to endocrine and biochemical/metabolic studies (55, 57). (Donald Gann at Johns Hopkins University had independently prepared an effective simulation for an endocrine system using a different mathematical approach.)

administered corticosterone in the rat was chronically varied over a wide range by 1) an inherent sex difference (female > male by 3-fold), chronic thyroid hormone injections, and thyroidectomy. The weight of the adrenal cortices (sum of adrenal weight/100 g body wt) was linearly dependent on the activity of the hepatic inactivating enzymes (\(\mu\text{M} \cdot 15 \text{ min}^{-1} \cdot 100 \text{ g body wt}^{-1}\)). Cortisone was the test substrate. Each data point is a group mean for \(~8–9\) animals. This striking result implied the action of a strong negative feedback control acting through plasma levels of the steroid. (This result is shown diagrammatically here. Full details are in Ref. 61 and provide the treatment details for each of the 9 groups. The intercept on the ordinate is the expected weight of the adrenal medulla.)

Fig. 2. Rate of ring A reduction of corticosteroids by liver set size of the adrenal cortex. The hepatic activity of \(\Delta^4\)-steroid hydrogenases that inactivate corticosteroids in the rat was chronically varied over a wide range by 1) an inherent sex difference (female > male by 3-fold), chronic thyroid hormone injections, and thyroidectomy. The weight of the adrenal cortices (sum of adrenal weight/100 g body wt) was linearly dependent on the activity of the hepatic inactivating enzymes (\(\mu\text{M} \cdot 15 \text{ min}^{-1} \cdot 100 \text{ g body wt}^{-1}\)). Cortisone was the test substrate. Each data point is a group mean for \(~8–9\) animals. This striking result implied the action of a strong negative feedback control acting through plasma levels of the steroid. (This result is shown diagrammatically here. Full details are in Ref. 61 and provide the treatment details for each of the 9 groups. The intercept on the ordinate is the expected weight of the adrenal medulla.)
Biological clocks. Studies of biological clocks had become a major thrust in physiological studies of dynamics at all levels, from organisms to gene expression, so Yates turned his attention to biological rhythms and methods of time series analysis for periodic behaviors (2, 3, 4, 16, 19, 27, 32, 43, 45, 46). The biological clock commonly chosen for study was the circadian rhythm, with its ~24-h period, but Yates thought that ultradian rhythms (periods < 24 h) might be equally important, although harder to catch in action, and may even be the primordial temporal organization at the start of terrestrial life (62). Furthermore, he had a theory of their significance and origins. That theory he called “homeodynamics,” an update on Cannon’s classical “homeostasis” (34).

From homeostasis to homeodynamics. By the 1970s, complexity had become a technical subject in physics, engineering, computation, and mathematics (more generally). Having worked so long with applications of engineering feedback control theory to physiological systems and on the extended approach with systems analysis, as noted above, Yates became convinced that something was always missing, namely, a physical basis for the many theories of biological regulations. He thought that the remedy might be found in the work of physicists A. Iberall and H. Soodak (10, 20, 53), called “homeokinetics.” It hinted that the missing dynamics could be found in the details of Navier-Stokes hydrodynamics. But, biology had turned into an information science, and there was difficulty in bridging between genetic information (which is static by itself) and dynamics (which is motion and change).

Starting with Cannon’s concept of homeostasis and Iberall-Soodak’s concept of homeokinetics, Yates undertook a synthesis of these themes, leading finally to his concept of homeodynamics (29, 40). It is a modification of homeokinetics and a modernization of Cannon’s homeostasis (35, 37), and Yates sees it as an instance of a strategic “physical biology” (as opposed to tactical biophysics). At a time when physicists are discovering the “mesoscopic” scale (between the quantum world and relativistic cosmology, i.e., the place where we live) and biologists are relabeling old ideas with new names (e.g., “functional genomics”), it is a two-dimensional topological object. Each cycle processes a packet of energy, and the largest packets lie in the ubiquitous circadian rhythms of living organisms.

A major feature of homeodynamics is the claim that energy throughput and transformations in persistent, complex, open thermodynamic systems will necessarily be temporally organized in a cyclic manner, at all levels of organization. Homeodynamics views biological time as an emergent property (39), and it invites an intellectual investment in “biospectroscopy.” The cycles are nonlinear, and, although they occur in three dimensions, their projections on two dimensions for spectral analysis have a limit cycle character. (Technically, a limit cycle is a two-dimensional topological object.) Each cycle processes a packet of energy, and the largest packets lie in the ubiquitous circadian rhythms of living organisms.

Prof. Yates had long felt challenged by the tension arising from the Bohr-like complementarity between information and dynamics in biological science. Each perspective is necessary but incomplete. Until the middle of the last century, dynamics (the study of functions and changes) outranked information (genes especially) in physiological sciences. Development, growth, organ functions, aging…they were all conceptualized chiefly in kinetic or kinematic terms. After 1953, of course, it all changed, and the era of genetic determinism (the “gene for . . .” syndrome) swept through biology, creating a situation at scientific meetings where the most common words heard as slides were shown became “. . .at the molecular level.” But, it’s a long way from genotype to phenotype; genes are static alone, whereas function, by definition, is dynamic. Today, with multiple RNAs modulating genes, and even with a “histone code” proposed, dynamics has come to the fore again, to Yates’s delight.

The UCLA Years (1980–2001)

People who made substantial and sustained contributions to the scientific activities of Yates’ laboratory or programs during the UCLA years are shown in Table 1.

In 1980, Yates became the first Director of the Crump Institute of Medical Engineering at UCLA, where he had joint appointments as Professor of Medicine and Professor of Chemical Engineering and was also the first holder of the endowed chair, The Ralph and Marjorie Crump Professorship of Medical Engineering. He held those three positions until 1988. After 1988, Dr. Yates continued to serve as Professor of Medicine at UCLA in the Division of Geriatric Medicine and Gerontology and devoted his time to both theoretical and clinical research in medicine, particularly in studies of aging.

Aging. Yates thought that it would be necessary to quantify rates of aging in well people over their mature years (ages 30–70 yr). With graduate student Mary Sehl, he undertook a meta-analysis of a larger data set on normal aging than had been previously addressed for the purpose. It revealed a nearly linear rate of loss of many forms and functions (18), with a median loss rate of 0.6%/yr (referenced to 100% capacities at age 30 yr). Such a result demanded a kinetic explanation. To that end, Yates reviewed most of the current theories of aging (38) and the association between time and aging (39) as well as the temporal organization of physiological systems more generally.

Homeodynamics supports a general theory of aging after maturity is reached (40, 47, 48) and also suggests a reconciliation between “use it or lose it” and “use it and lose it” as exercise loads are increased. With his research associate Laurel Benton, he presented a new theory of aging in the Handbook of Physiology (48). According to Yates, a consequence is that lifetime energy budgets can be visualized as an attenuated ellipsoid, the envelope of a helix that combines the metaphors of “time as a cycle” with “time as an arrow.” The attenuation represents effects of aging in organisms that reach a fixed size in maturity.

In 2003, he accepted a position as a Scientific Advisor and member of the Board of Directors for The John Douglas French Alzheimer’s Foundation, and he is currently active in those positions, focusing on age-associated diseases generally and dementias especially. His current role is to identify funding opportunities for the foundation’s award program that might be rejected by NIH study sections as too premature or risky. Three years ago, he established a Career Development Award for the foundation that has proved very productive. Four young scientists receiving the award have already published distinguished research.

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Semiotics. A chance encounter with Thomas Sebeok, a
doyen in the polyglot semiotics community (signs, signals, and
significance), introduced Prof. Yates to varieties of scholarship
new to him. He saw in them the possibility of framing the
information/dynamic dichotomy in a fresh way. From 1984 to
2002, responding to invitations from the semiotics community,
he published 12 papers of interest to them, 3 of which are
especially relevant to the tension between information and
dynamics as explanatory modes (30, 41, 51). He became an
advisor to Sebeok’s Semiotics academic program at Indiana
University.

Self-organizing systems. Of all his scientific activities and
achievements, Prof. Yates especially values the book he edited,
and contributed essays to, entitled Self-Organizing Systems:
the Emergence of Order (31). It has a vitality arising from the
fact that it was one of the first books with great technical depth
dealing comprehensively with various complex systems. It was
the product of the international conference, under the same
name, that Yates organized in 1979, in Dubrovnik, Croatia.
Those in attendance were distinguished in many fields: math-
ematics, control engineering, life sciences, physics, chemistry,
computation, and philosophy . . . and Yates insisted that they
write their contributions after they got home from the meeting,
so they could take advantage of what they had learned there.
(He wanted no stale “boilerplate” dropped off at the meeting
itself merely to justify the air fare and all other expenses he had
found funds to cover.) It took 7 yr to get all the manuscripts in
hand. Each was reviewed by two others who had attended,
chosen by the authors themselves, and, finally, also edited by
Yates.

The ALZA years (1969–1997)

Yates has had a special interest in the controlled delivery of
therapeutic drugs. From 1969 to 1997, he served as a Consult-
ing Principal Scientist for the ALZA Pharmaceutical Com-
pany, specifically devoted to controlled delivery formulations.
Over the course of 28 yr, he participated in research leading to
many of ALZA’s unique products (42). However, his favorite
effort was the development of an osmotic minipump that could
be implanted subcutaneously to deliver a constant infusion,
even into brains, while the animals were not tethered to
external pumps and were free to move about normally. These
minipumps have been extraordinarily valuable for pharma-
ological studies. At latest count there have been >10,000
publications citing their use. (Table 1 lists the names of the
minipump team.)

Yates retired from ALZA in 1997, but he continues to rely
on insights from control engineering in the development of
pharmaceuticals through controlled delivery. Some of his rel-
vant articles are Refs. 25, 26, 33, 36, 41, 44, and 56.

Chief Society Memberships

Yates’ chief society memberships include the following:
• The American Association for the Advancement of Sci-
ence (Fellow)
• APS
• The Endocrine Society
• BMES (founding member)
• The Gerontological Society of America
• The American Society of Hypertension

Special Service to APS

“Sectionalizing” the American Journal of Physiology. In
1975–1976, acting on a request from the APS Council, the
three-man Publications Committee [Al Fishman (chairman),
Paul Horowitz, and Gene Yates, assisted by Steven Geiger
(Publications Manager) and Brenda Rauner] “sectionalized”
the massive American Journal of Physiology in response to the
needs of increasing specializations within the parent science.
Overcoming a number of practical difficulties, they created
the following specialty journals and appointed editors: American
Journal of Physiology-Cell Physiology, American Journal
of Physiology-Endocrinology and Metabolism, American
Journal of Physiology-Gastrointestinal and Liver Physiology,
American Journal of Physiology-Heart and Circulatory Physi-
ology, and American Journal of Physiology-Renal Physi-
ology (respiratory, thermal, and adaptive processes were left within
the Journal of Applied Physiology). When the job was done, Yates
asked: “But where would Cannon have published ‘homeosta-
sis’?” In answer, he proposed a sixth section, viz., American
Journal of Physiology-Regulatory, Integrative, and Compar-
ative Physiology. It was immediately adopted, with Yates as the
Editor.

For his new journal, known familiarly as AJP-Regu, Profes-
son Yates established three departments not found regularly in
any other APS journal: Editorials, Invited Opinions, and Mod-
eling Methodology Forum (which included statistics). Yates
assumed responsibility for the first two departments and re-
cruited Joseph DiStefano, 3rd, to manage the modeling. During
the 7 yr of his editorship, Prof. Yates published 23 editorials
designed to provoke thoughtful reflections and debates about
the character of modern physiology and its future in the
triumphant era of molecular biology.

Some Advisory Roles

Dr. Yates has served on various advisory panels for NIH,
NSF, the Food and Drug Administration, NASA, and the
Federation of American Societies for Experimental Biology
(FASEB) as well as for the societies mentioned above. For 3
yr, he was Chairman of the FASEB Meetings Committee
responsible for their annual Spring Meeting. For 7 yr, he served
as a member of the External Advisory Board of the NSF Center
for Biological Timing at the University of Virginia. He was
also a science advisor to the National Space Biomedical Re-
search Institute, associated with NASA, which is planning for
a manned trip to Mars. (He just completed 8 yr of service for
the National Space Biomedical Research Institute and retired in
March 2008.)

He was a member of the Physiology Training Committee of
the National Institute of General Medical Sciences, NIH
(1964–1969); a member of the Medical Scientist Training
Committee of the National Institute of General Medical Sci-
cences (1971–1973); a member of the FASEB Awards Com-
mittee (1978); NSF/American Institute of Biological Sciences
Task Force Leader for Medical Engineering, assigned to Egypt
and Yugoslavia (1975–1978); a member of NASA’s early
Space Biology panel (1979–1980); a member of the Neuro-
logical Diseases and Stroke Information Program Advisory
Committee (National Institute of Neurological and Commu-
nunicative Disorders and Stroke, NIH) (1975–1979); a member
of National Research Council Human Resources Commission,
Basic Biomedical Sciences (1979–1981); and a member of the Special Study Section, Mathematical/Computational/Theoretical Neuroscience (National Institute of Mental Health, Alcohol, Drug Abuse, and Mental Health Administration) (1990–1991).

Some Mentors, Colleagues and Other Scientists Who Were Especially Influential

In reflecting on the above career trajectory, Prof. Yates made the following comments:

During my career I have encountered and benefited from the experience and wisdom of many scientists, including: Cliff Barger (skills in gentle handling of chronic preparations in animals who remained unstressed), John Pappenheimer (introduction to transport phenomena), Bob Brennan (computer simulation of engineering control systems), Tom Sebeok (signs, symbols and significance), Arthur Iberall (a new physics for complex systems), Phil Anderson [needed balance between reductionism (analysis) and holism (synthesis) for many comprehensive descriptions in sciences, and showing that they are not technical inverses], Howard Pattee (information versus dynamics in biology), Bob Rosen (a mathematics for complexity), Alex Zaffaroni (adding control to chemistry in pharmaceutical science), Walter Bortz (showing me that good medical science can be an effective basis for sensible public health policies), and Larry Young (countermeasures against risk factors for long-duration, human space flight). I owe them all (and many others—including students and post-docs) profound thanks for the joy and passion their insights have added to my professional life.

Advice to Young Scientists

When asked to make suggestions to those starting a career in physiology, Prof. Yates commented that “I value four classical examples of advice to young scientists—they all influenced me strongly:

- **Santiago Ramón y Cajal. Advice for a Young Investigator.** (The original was based on lectures in 1898 in Spanish; the current edition is as follows: translated by Swanson N, Swanson LW, Boston, MA: MIT, 1999).
- **P. B. Medawar. Advice to a Young Scientist** (Jackson, TN: Basic Books, 1979).
- **Claude Bernard. An Introduction to the Study of Experimental Medicine** (in French, 1865; the current edition in English is as follows: Mineola, NY: Dover, 1957).

I do notice certain common attributes among my favorite colleagues in science: all have deep respect for rules of evidence, humility in the face of what they don’t (yet) understand, [and] courtesy toward colleagues and openness in discussions of their own past and present work."

A list of a few senior colleagues whose current work and interests continue to influence Yates’ studies is shown in Table 2.

### Table 2. Senior colleagues whose current work and interests continue to influence Yates’ studies

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Walter Bortz, 3rd</td>
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<td>Laurel Benton Yates</td>
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<td>John Urquhart</td>
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<td>Joseph Zbilut</td>
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<td>David Lloyd</td>
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<td>David Shannahof-Khalsa</td>
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<td>Felix Theeuwes</td>
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<td>Bruce Miller</td>
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<td>George Martin</td>
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<td>Leonid Gavrilov</td>
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<td>Joseph DiStefano, 3rd</td>
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<td>Richard Veech</td>
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Summary

The samples of his research shown in the bibliography attest to Prof. Yates’s wide-ranging curiosity and his originality. As a result, he had been recruited to occupy the executive position of five departments of physiology or biomedical engineering (accepting one) and two biomedical research centers/institutes. He has founded and edited three technical journals for three societies. His seminars in the then-nascent fields of “systems biology” and computer simulations of endocrine and metabolic system control led to numerous invitations to develop his ideas in many book chapters, always with whole organism physiology in mind. He was early to recognize that “complexity” was becoming a technical subject of great interest, and he organized international conferences to encourage its development in biology. His research has involved studies with experimental animals and clinical studies in human beings, computer modeling, and the creation of a theoretical extension of Cannon’s 1926–1930 “homeostasis” concept, to take advantage of modern advances in physics, engineering, mathematics, and biology. On the practical side, he helped ALZA with the development of novel controlled delivery systems for therapeutic agents and the National Space Biomedical Research Institute/NASA with countermeasures against the deleterious physiological effects of long space flights. He has argued vigorously for a “strategic physical biology” to go beyond tactical, conventional biophysics. In doing so, he has enjoyed the collegiality of some outstanding physicists.

It seems appropriate to close this summary with a remark by Philip Anderson (Nobel Prize in Physics, 1977), who wrote that his meetings with the Yates’ group had stimulated his interest in biology, and he thought of “Gene Yates as a leader of thoughtful biology.”
REFERENCES


Yates FE, Maran JW. Stimulation and inhibition of adrenocorticotropic release. In: Handbook of Physiology. The Pituitary Gland Ad Its Neuroend...


