CONTENTS

USA NATIONAL COMMITTEE FOR
THE INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES

ANNOUNCEMENT OF TRAVEL AWARDS

The USA National Committee for the International Union of Physiological Sciences (IUPS) is sponsoring a travel grant program to benefit American scientists who could not attend the XXVI International Congress of Physiological Sciences in New Delhi, India, 20-26 October 1974, without such assistance. A limited number of grants will be available. Those eligible for awards are qualified scientists who are citizens or permanent residents of the United States. Each applicant will be judged on the merit of his contribution to the Congress in New Delhi, considering his training, experience, and potential, as well as a reasonable representation of age groups. Grants will ordinarily be limited to the lowest group fare available plus domestic fare.

Requests for application forms should be addressed to:

USA National Committee for IUPS
Room 342
Division of Medical Sciences
National Research Council
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Deadline for receipt of applications is 1 December 1973

WALTER E. GARREY

1874 - 1951

Dr. Walter E. Garrey was born in Reedsville, Wisconsin, April 7, 1874. He received his early physiological inspiration under the great Jacques Loeb. He assisted Professor Loeb in organizing the first physiology course at Woods Hole in 1899 and continued as instructor in the course until 1925. Dr. Wallace Fenn remarked in a biography of Dr. Garrey that he had had the good fortune to be a student in that course in 1915 and profited greatly from his contacts with Dr. Garrey. He found him to be an inspiring teacher and a warm friend. His degrees are B.S., Lawrence College, 1894; Ph.D., University of Chicago, 1900; M.D. Rush, 1909. He did graduate work in Berlin and Paris in 1898 and 1900.

On returning from Europe in 1900 he was at once appointed Professor of Physiology and Biochemistry in Cooper Medical College, later incorporated into Stanford University. In 1910 he was advanced to the staff at Washington University, St. Louis, in 1912 to Tulane, and to Vanderbilt in 1925 where he was Professor of Physiology and Chairman of the Department until he retired in 1944.

Dr. Garrey always had an interest in problems of scientific and educational import. He served on the Medical Research Council, Medical Division, 1929, also on the Board of Medical Examiners, and was a Trustee of the Marine Biological Laboratory, Woods Hole, the biological Mecca of the United States.

Dr. Garrey's researches were numerous and covered a wide range of interest. He contributed to the early researches that established artificial parthenogenesis. His papers on salt balance and on tropisms were pioneer. His researches on mammalian cardiac fibrillation are classic. He was first to clearly describe the phenomenon of fibrillation. He invented a new term "circus movements" to describe the fundamental nature of this unique form of cardiac irregularity.

Dr. Garrey discovered the predominant homolateral action of the vagi on the heart, and the localization of vagus action in relation to cardiac irregularities. He advanced a theory of inhibition of nerve cells; demonstrated reduced oxidations during inhibition; investigated the nature of the rhythm of the neurogenic heart of limulus, and studied parathyroid tetany. He contributed a study of adaptation of salivary secretion to diet and has to his credit other titles too numerous to mention.

Dr. Garrey was elected to membership in the Society in 1910, he was on Council in 1915-16 and 1924-28, and was elected to serve as President at the semi-centennial meeting in 1938. He was also chairman of the section on Pathology and Physiology of the American Medical Association. He was therefore in the enviable position of recognized national leader in his profession as expressed by the votes of both his medical and physiological colleagues.

Dr. Garrey died June 15, 1951. An obituary by F. P. Knowlton was published in the "Biological Bulletin" (103: 13, 1952): "An athlete in his younger days, he remained tall and erect. With his head of white hair he was a noteworthy figure at any gathering."

HONORARY PRESIDENT, WILLIAM T. PORTER

Dr. Porter was made honorary president during the presidency of Walter E. Garrey for the special purpose of honoring him at the time of the Semicentennial Celebration of the founding of the Society. He was elected to membership in the Society in 1891. He was an unostentatious but most effective contributor during his forty-six years of life in the American Physiological Society. A full account of Dr. Porter's career and his many generous contributions to the Society are given in "The Physiologist" (4: 28, 1961).

Taken from History of the American Physiological Society Semicentennial 1887-1937 and The Third Quarter Century 1937-1962

TEACHING SESSION: Computer Assisted Education

The Education Committee of the American Physiological Society will sponsor a teaching session entitled "Computer Assisted Education" during the FASEB meeting in Atlantic City, N.J. (April 15-20).

The program was organized by the session chairman, Dr. C. S. Tidball, Ph.D., M.D., Henry D. Fry Professor of Physiology, at the George Washington University Medical School.

Wed. A.M. - Convention Hall - Ballroom

Chairman: C. S. TIDBALL

PART I. Welcome and Computer Fundamentals

9:00 Introduction to Teaching Session. C. S. Tidball. George Washington Univ.

9:15 Rudiments of computer assisted instruction. H. O. O'Neill. Univ. of Texas, Austin.

PART II. Challenges of CAI development.

10:00 Hardware. R. J. Seidel. Human Resources Res. Organization (HumRRO), Alexandria, Va.

10:20 Software. G. O. Barnett. Massachusetts Gen. Hosp.

10:40 Courseware. C. V. Bunderson. Brigham Young Univ.

11:15 Panel discussion with audience participation.

The panel will consist of the main speakers with the addition of the following: H. A. Wooster, P. Tenczar, and J. V. Griesen. Lister Hill Natl. Ctr. for Biomed. Communications, Univ. of Illinois, Champaign-Urbana, and Ohio State Univ.

PART III.

1:30 Short presentations of Application Programs

PART IV.

3:00 to 5:00 Demonstrations of Application Programs at individual locations (simultaneous).

Cardiopulmonary resuscitation program (MUMPS)*. G. O. Barnett. Massachusetts Gen. Hosp.

Electrolyte and acid-base equilibrium (MUMPS). H. L. Bleich. Beth Israel Hosp.

Artificial intelligence approach to computer aided clinical diagnosis. J. D. Myers. Univ. of Pittsburgh.

Simulation of nerve action potential experiment. (PLATO IV). L. Barr. Univ. of Illinois, Champaign-Urbana.

Physiology (diffusion, osmosis, and membrane potentials). (Coursewriter III). J. V. Griesen. Ohio State Univ.

Computerized random item bank. (Coursewriter II). G. Drennon. Univ. of Illinois Med. Ctr., Chicago.

MEDLEARN. (FOCAL-10). C. S. Tidball. George Washington Univ. Med. Sch.

Clarity and coherence in paragraphs. (TICCIT). C. V. Bunderson. Brigham Young Univ.

Guess the Animal. (BASIC - EduSystem 25). D. H. Ahl. Digital Equipment Corp., Maynard, Mass.

Teaching renal physiology by Minicomputer. (CAIBO-PDP-8). C. H. Wells. Univ. of Texas Med. Br., Galveston.

*The item in parenthesis refers to the computer language or system for which the Application Program was written.

The list of actual Application Programs above was incomplete at press time.

A portion of the expense of organizing this session was borne by a contract which the American Physiological Society has with the National Medical Audiovisual Center in Atlanta, Ga.

APS FALL MEETING - ROCHESTER, NEW YORK

AUGUST 20 - 24, 1973

The 24th annual "Fall" meeting of the APS will be held jointly with the International Symposium on Dynamics and Controls in Physiological Systems on August 20-24th at the University of Rochester.

The refresher course, which is scheduled for Monday, August 20th, is being organized by Dr. Bodil Schmidt-Nielsen on the subject "Physiological Adaptations to the Environment." This program will be divided in three parts: Altitude and Air Pollution, Osmoregulation, and Temperature Regulation.

On Tuesday there will be two symposia. In the morning Dr. Leon Farhi will chair a session devoted to "Diffusion of Gases in the Gas Phase of the Alveoli." In the afternoon the topic will be "Molecular Mechanisms of the Sodium-Potassium Pump" and is being planned by Dr. Joseph Hoffman.

The Dynamics and Control Symposium will begin on Wednesday and continue through Friday. This symposium was previously scheduled to take place in Rochester the week before the APS meeting which had been planned for Montreal. Now that the APS meeting has been moved to Rochester, it was decided to have a single registration in order to encourage interchange between engineers and physiologists. This symposium has the joint sponsorship of the International Federation of Automatic Control, American Society of Mechanical Engineers, APS, and International Union of Physiological Sciences. Drs. Gerald H. Cohen and Edward F. Adolph are general chairmen. Papers will be presented in several concurrent sessions. A major purpose of the symposium is to focus the attention of engineers and physiologists on topics of common interest. A preprint of the symposium will be available at the time of the meeting. Those who purchase this volume will receive an addendum containing the discussion at a later date.

The traditional scientific sessions with 10 minute presentations will begin on Tuesday August 20th and end at noon on Friday. The deadline for the receipt of abstracts is June 1st.

In addition to the scientific aspects of the program, registrants and guests will have an opportunity to explore Upstate New York and the City of Rochester. Four one-day trips will be offered: Niagara Falls, a visit to Letchworth Park (the Grand Canyon of the East), a trip to a local winery in the Finger Lakes region, and an architectural tour of Rochester. The Local Committee will also try to facilitate visits to interesting and unique local places such as the Eastman Photographic Museum, the Strasenburg Planatarium, Rochester Art Gallery, and shops which feature the work of local craftsmen and artists.

The athletic facilities of the University will, of course, be available to registrants and guests. The dormitories which will be used for housing are particularly suitable for this meeting, for they have many places

to visit with friends and informal conversations.

There will be a reception on Monday evening. Beer will be served outdoors, but Rochester weather may dictate a retreat to the field house. The annual Society dinner is scheduled for Wednesday evening. On Tuesday and Thursday evenings we plan movies (don't expect the latest) on campus for those who wish to retreat from the scientific scene for a while.

As Rochester is on the east-west flyway, it is an easy place to get to by plane (American, Allegheny, and United). However, local resources are attractive for walking, swimming, and general site-seeing, and it is worth considering a family trip by car.

The local members of APS are privileged to serve as your hosts. The last meeting of the APS in Rochester was in 1946, and we again look forward to welcoming our many old and new friends.

Albert B. Craig, Jr.
Chairman, Local Committee

SEVENTEENTH BOWDITCH LECTURE

Neural and Humoral Factors in the Temporal Organization of Behavior

FELIX STRUMWASSER
Division of Biology
California Institute of Technology

This paper is concerned with an ongoing search for principles operating in the nervous system that organize behaviors, particularly those that are periodic. Most of the research work that I will describe has been carried out on the sea hare, Aplysia californica (Mollusca: Opisthobranchia). The fact that we study the neurophysiology, neurochemistry and behavior of the sea hare raises the question as to whether the principles that organize periodic behaviors in this simpler organism are applicable to the higher vertebrates. I believe that the answer to this question is clearly yes. The arguments for this attitude are based on the available evidence which indicates that the nature of neuronal and glial mechanisms in nervous systems is amazingly conservative.

The Conservative Nature of Neuronal and Glial Mechanisms

The mechanisms of conduction of an impulse along a neuronal membrane or a muscle membrane appear to be quite similar across all of the phyla. The sequential activation of a specific electrically excitable sodium or/and calcium channel followed by the activation of an electrically excitable potassium channel generally accounts for the formation of an action potential, while the cable-like properties of the cylindrical processes allow propagation. Transmission between neurons or neuron and effector, whether electrical or chemical, appears to possess similar mechanisms across phyla. Electrical synapses depend on specialized junctions (gap junctions) in which the extra-cellular space is minimized (Robertson, 1963; Pappas et al., 1971). The chemically transmitting junctions possess vesicles, located in the presynaptic terminal, which have been directly shown in many cases to store a specific transmitter substance. The mechanisms by which transmitter substance is released from the presynaptic nerve terminal include, where examined, a calcium dependent step which appears to be universal at all chemical synapses (Katz, 1969).

There is a wide overlap in the nature of transmitter compounds in the various phyla. The overlap is so extensive that no single transmitter compound can be said to be unique to a particular phyla. Thus acetylcholine is used as a transmitter substance not only for vertebrate neuromuscular junctions but at junctions in certain crayfish muscles (Futamachi, 1972) as well as in the central nervous system of molluscs (McCaman and Dewhurst, 1970; Giller and Schwartz, 1971; Gerschenfeld, 1971; Kehoe, 1972). GABA, the inhibitory transmitter at crustacean neuromuscular junctions, appears to be utilized also as an inhibitory transmitter in vertebrate cerebellum (Curtis and Felix, 1971) and an excitatory transmitter in vertebrate spinal cord (Barker and Nicoll, 1972). Norepinephrine, dopamine and serotonin are widely distributed

in nervous systems of different phyla (Rude et al., 1969; Geffen and Livett, 1971; Hildebrand et al., 1971). Glycine, one of the presumed inhibitory transmitters in the spinal cord of vertebrates (Werman et al., 1968), so far has not been reported to be a specific transmitter among invertebrates. Not only the wide overlap of transmitter compounds in the various nervous systems, but also the common mechanisms of the synthesis of these compounds, their uptake from the presynaptic terminal and their degradation are all further evidence of the conservative nature of neuronal mechanisms.

There are strong pharmacological arguments that membrane receptors have remained stable throughout evolution. Tetrodotoxin (TTX) and the tetraethyl ammonium ion (TEA) have highly specific blocking effects on the electrically excitable sodium and potassium channels respectively in neurons in all of the phyla so far studied. Cholinergic (nicotinic) postsynaptic receptors are blocked by Curare whether they are of vertebrate or molluscan origin. Similarly, GABA receptors are blocked by bicuculline whether they are of vertebrate or crustacean (McLennan, 1970) origin.

Axoplasmic transport appears to be a common feature of all neurons; drugs, such as colchicine, that affect this transport do so whether they are applied to invertebrate or vertebrate preparations (Fernandez et al., 1970; McClure, 1972; Ochs, 1972). The little that we know about glia in nervous systems tells us that they are depolarized by the potassium released by adjacent neurons as a result of their activity. This potassium mediated depolarization of glia appears to apply to invertebrate as well as vertebrate nervous systems (Kuffler and Nicholls, 1966; Dennis and Gerschenfeld, 1969). The evidence presented that neuronal and glial mechanisms are basically conservative suggests that when new mechanisms are discovered, they should be considered to be of more general significance rather than specific to the species or phylum.

Specialized Neurons: Oscillators and Neurosecretors

The remainder of this paper is concerned with the presence of circadian and faster oscillators (pacemakers) within single neurons and groups of neurons in specialized parts of the sea hare nervous system. One of the circadian oscillators that will be described is known to play a role in the sleep-waking cycle of this organism. I would suggest that similar neurons exist in the vertebrates including mammals; these are of course more difficult to find and to study in such preparations. The molecular mechanisms of any circadian oscillator are really not known. However, some progress has been made in an analysis of those membrane and biochemical mechanisms that may be unique to pacemaker neurons. Since certain of these pacemaker neurons are also circadian in their discharge rates, the former mechanisms may be of eventual importance in understanding the nature of the circadian oscillator.

The second generalizable point of this paper is that specialized nerve cells can secrete polypeptides that control behavior. In the sea hare a specific group of neurons secretes a polypeptide in response to

copulation. This polypeptide has remarkable effects in organizing the subsequent temporal behavior of the sea hare, including the production of an egg string and its storage on the substrate. The fact that specialized nerve cells might secrete polypeptides to trigger certain behaviors may be general to other phyla including the vertebrates. There is some evidence that mammalian sleep may be mediated by a small molecule (< 500 mol wt) released in the brain and that a brain peptide exists which causes hyperactivity (Fencl et al., 1971).

Sleep-Waking Behavior in the Sea Hare

As in most multicellular organisms the sea hare, Aplysia californica, has a circadian rhythm of locomotor activity (Strumwasser, Lu and Gilliam, 1966; Strumwasser, 1967b; Kupfermann, 1968; Jacklet, 1972). Time lapse photography has been used to study the behavior of the animal during its quiet and active period (Strumwasser, 1971). The sea hare is day active and becomes quiescent around the offset of light. During the night the sea hare makes postural adjustments, but most usually does not shift from a particular position in the home tank. Intermittent movements during the night are apparent in the head region of the animal, the rhinophores and the anterior tentacles. The initiation of locomotor activity occurs around the light onset. The anticipation of light by certain animals already suggests that there is built into the organism an endogenous oscillator. However, more convincing evidence for this point of view comes from experiments in which the animal is suddenly exposed to a constant light or a constant dark schedule. Animals shifted from a light-dark cycle to constant light still show circadian sleep-waking cycles for at least several days (Strumwasser, 1971).

Tracking locomotor movements and analyzing their periodicities. These earlier experiments raised the obvious question as to the location and nature of the endogenous oscillator in the organism. In order to study the effects of lesions of the nervous system on sleep-waking behavior in this or any organism, quantitative methods are needed for tracking the movements of the animal and analytic tools are needed to describe the nature of the periodicities that are present in the animal's rhythms. A non-contact method of locating the sea hare in its marine environment is utilized in my laboratory. A television camera transduces the visual scene into analog electrical information which is then analyzed by a special video encoder that essentially pattern recognizes the sea hare. The position coordinates X and Y, of the sea hare, are fed into a digital computer which writes the coordinate data for each day at midnight onto magnetic tape. This data on magnetic tape can then be analyzed in various ways. Typically, averages of several days of locomotor movements, periodograms and power spectra are used to analyze the data.

The average activity, the periodogram and the power spectra of two consecutive nine day periods are shown in Figure 1 for an intact sea hare. The average activity which is expressed in meters per hour on the ordinate clearly shows that this animal is quiet in the dark and very active during the light period. During the first nine day period (calendar days 152-160) the initiation of locomotor activity is very close to

the onset of light, and the termination of activity starts prior to light offset. However, in the subsequent nine day period (calendar days 161-169) the animal initiates its activity before light onset and although activity declines prior to the offset of light it is continued for a short while after the lights are off.

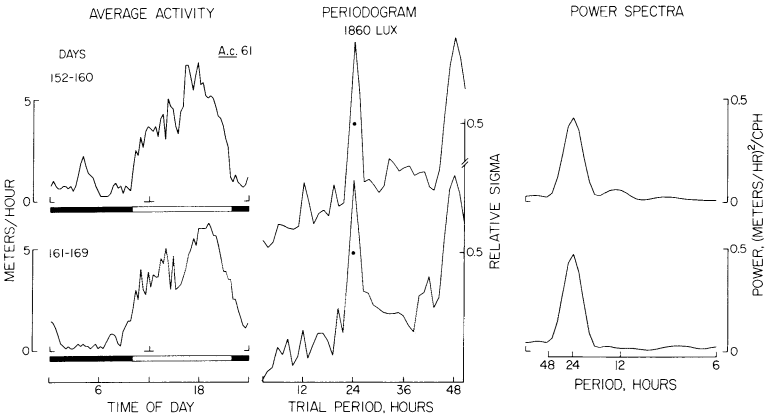

Fig.1. Three methods of analysis of locomotor activity in Aplysia californica. The left-most column shows the average activity. The numbers under days are the calendar days over which the data frame was obtained. The average activity is expressed as meters per hour. The average activity curve has 18-minute resolution and was generated by taking a stationary motion average from nine coordinate pairs spaced at 2-minute intervals. The abscissa is time of day with 0 representing midnight of a calendar day. The photo-period that the animal was exposed to was 12 hours of darkness followed by 12 hours of light and the timing is shown immediately below the graph of average activity. The middle column is a periodogram analysis of the nine inclusive days of movement. The ordinate of a periodogram is a relative sigma (standard deviation) - see text. The trial period scans from 2 hours and 24 minutes (that is eight 18-minute data points) to 50 hours and 24 minutes. A large dot has been positioned at 24 hours and 0.5 relative sigma. The right-most column is a power spectral analysis of the same data string. The ordinate is expressed as power in (meters per hour)^2 per cycle per hour. The abscissa scans from 216 hours to 6 hours. The data group size is 3 hours and the maximum lag is 2.25 days. The format of this figure is continued in Figures 2,3, and 4 with the exception that the power spectral column has not been shown.

The periodogram in this illustration is expressed as a relative sigma and as a function of a trial period scan from approximately two hours to 50 hours with 72 minute resolution. The periodogram is obtained by arranging each 9 day data array into a matrix whose width is the trial period. At each trial period the columns of data are averaged and the standard deviation of the column means are expressed relative to the standard deviation of the unordered matrix, giving rise to the relative sigma (Panofsky and Halberg, 1961; Enright, 1965; Strumwasser,

Schlechte and Streeter, 1967). The periodogram for this animal clearly shows two large relative sigma peaks for each of the nine day periods. These peaks are located at 24 hours and 48 hours on the abscissa (trial period). The peaks for this animal at the 24 hour trial period are relatively high (0.82 and 0.78 respectively). This is clear evidence that the animal was well entrained to the light-dark cycle. Other than the harmonic peak at 48 hours there are no other undulations in the periodogram which suggest any other contributing (e.g., ultradian) oscillator to this sleep-waking cycle. The power spectrum which is a Fourier transform of the autocorrelation function (Blackman and Tukey, 1959) and has units of power expressed here as $(\text{meters/hr})^2/\text{cycle/hr}$ also shows the dominant frequency to be circadian. All of the results that I will mention in this paper have been checked by power spectra and periodograms, although for the sake of brevity in both the figures and the text I shall refer only to periodogram analysis.

The eyes mediate entrainment and synchronization of the sleep-waking cycle. The isolated eyes of Aplysia have been shown not only to respond to light but also to possess a circadian rhythm of optic nerve impulse discharge during sustained darkness (Jacklet, 1969a; Eskin, 1971). The fact that a circadian oscillator is already built into the neural mechanisms of this eye suggested that the eye might play an important role in either driving or synchronizing the circadian rhythm of locomotion, besides being involved in entrainment of locomotion by light-dark cycles in the environment.

The stability of a sham operated sea hare is indicated in Figure 2. One eye, the right eye, was removed from the sea hare as well as a small piece of skin near the left eye. The animal was tracked in the locomotor system for some 100 days. The data shown in this figure spans 72 inclusive days. The topmost frame shows 21 days of data, while the second and third frames show the first 11 and the next 10 days of this 21 day period. The long term average clearly shows anticipatory activity prior to light onset as previously mentioned. The periodograms clearly show that the animal is entrained since the peaks are all at 24 hours and are large. The last frame shows the last 10 days of this 72 day period. Anticipatory activity prior to light onset is not obvious but entrainment is still present and good. The loss of one eye clearly does not appear to influence entrainment and the ability of the animal to express a normal amplitude and day-active circadian rhythm.

Eventual desynchronization by blinding. The effects of removing the two eyes of the sea hare are quite different. Figure 3 shows four 6-day frames. The first two frames are control periods. The control period average activity clearly shows that the animal is normal, that is, day-active and quiet at night. The periodograms show that the animal is clearly entrained to the 24 hour photoperiod (relative sigmas are 0.69 and 0.76 respectively). The last two frames show the behavior of the animal starting on the third day after eye removal. The first 6-day frame after eye removal shows quite clearly that the animal is no longer entrained to the 24-hour cycle, the period being 28 hours. The subsequent 6-day frame which starts at 13 days after eye removal shows

no obvious circadian rhythm. All the peaks that are present are close to the noise level but there are small peaks at 12, 24, 27.5, 38.4, 42 and 48 hours. This pattern of periodogram is best described as desynchronized. More detailed case histories are to be found in a paper in preparation (Strumwasser and Schlechte). Typically the results of removing both eyes in moderate intensity light (approximately 400 lux) are that sea hares are no longer entrained and ultimately the circadian free running rhythm of sleep-waking becomes desynchronized.

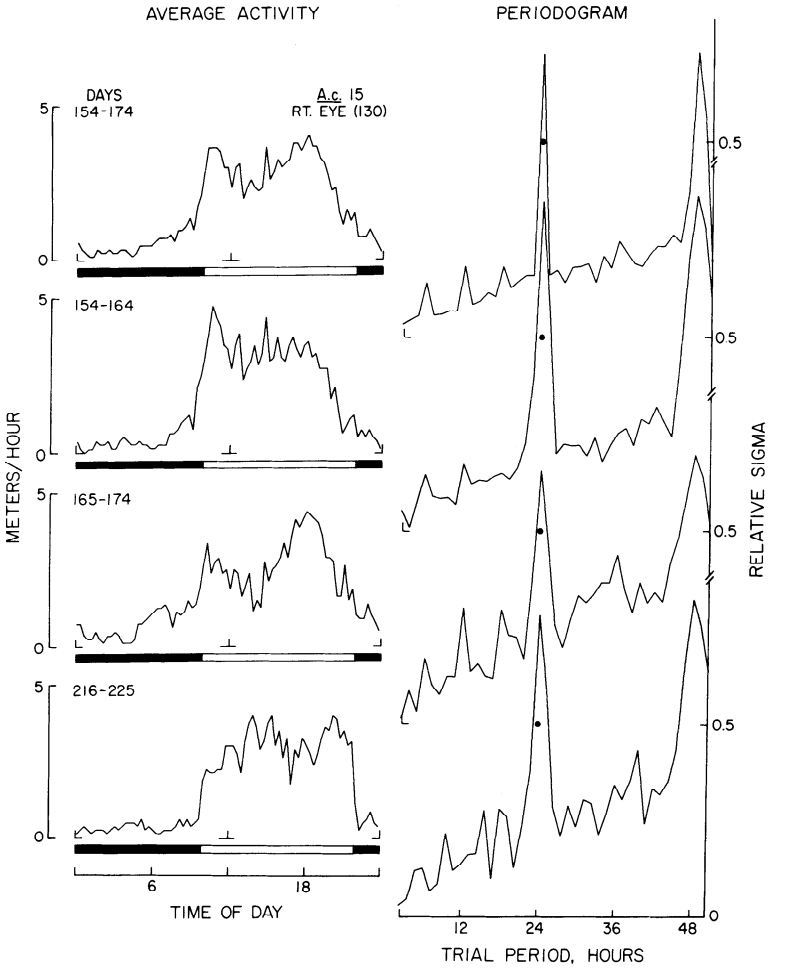

Fig.2. The average locomotor activity and periodogram analysis of a sea hare after removal of right eye (on day 130). A small piece of skin in front of the left eye was also removed at the same time. The data in this figure spans 72 days. Data for days 175-215 are not shown. (The first frame starts 24 days after the operation. Light intensity was 390 lux.) (See Figure 1 for further details.)

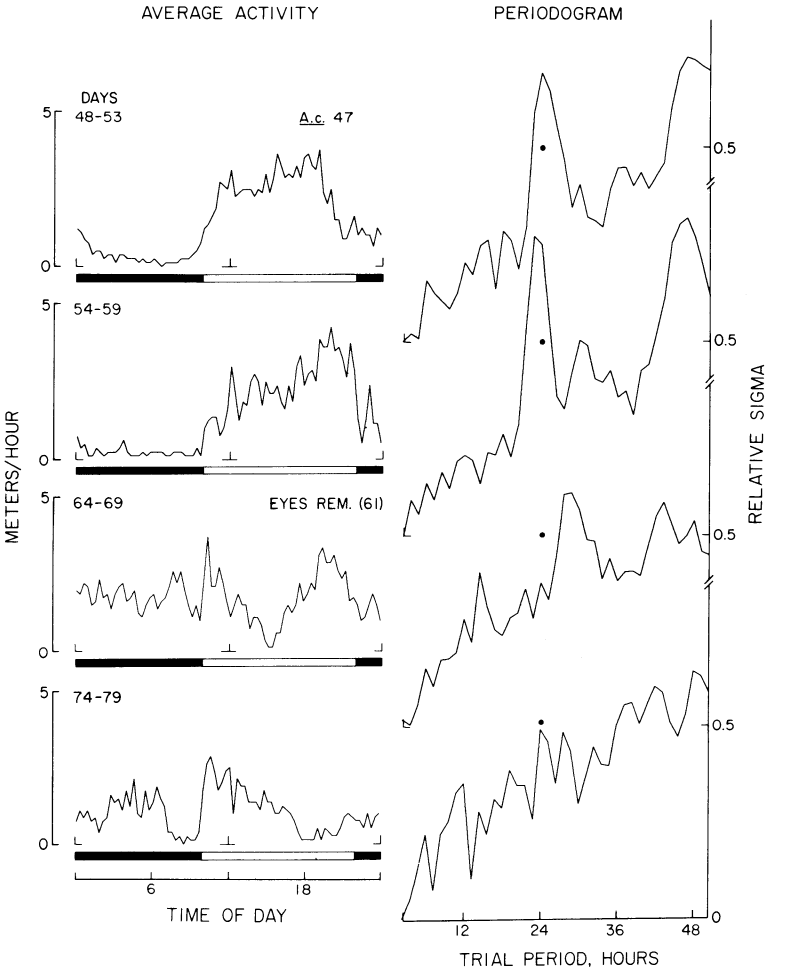

Fig.3. The average locomotor activity and periodogram analysis of a sea hare before and after the removal of both eyes. The first two rows of data were taken before removal of the eyes. Twelve inclusive days are contained in this period. This period terminates 2 days prior to eye removal. The experimental data frames began 3 days after eye removal. The light intensity was 350 lux. (See Figure 1 for further details.)

There is some evidence for a secondary photoreceptor system in Aplysia californica that does not involve the eyes (that is, is extra-retinal; cf. Bloch, 1971). If a freshly blinded animal is exposed to bright light (approximately 1800 lux), the circadian rhythm can be en-

trained. However, animals that are blinded for more than five or six weeks do not show this response, suggesting that the secondary photoreceptor system is perhaps dependent for its integrity on the presence of the eyes. Perhaps the secondary photoreceptor system becomes nonfunctional or degenerates in the absence of the eyes and this process may take a few weeks.

The parieto-visceral ganglion is not essential for the circadian locomotor rhythm. The parieto-visceral ganglion (PVG) of the sea hare is known to contain a particular neuron with an endogenous circadian oscillator (Strumwasser, 1965, 1967a, b; Lickey, 1969, 1971). In addition, there are unidentified neurons in this ganglion that have been demonstrated to possess circadian oscillations in organ culture (Strumwasser, 1967b). It has recently been found quite possible to remove this ganglion in the sea hare and thus to determine the contribution of the ganglion toward the sleep-waking cycle (Strumwasser, Schlechte and Bower, 1972). Figure 4 shows 42 days of locomotor activity in a sea hare in which the parieto-visceral ganglion had been removed. The first frame starts 22 days after the ganglion had been removed and is a run in constant darkness. The 8 days of this frame clearly show in the periodogram that the animal is capable of producing a free running circadian rhythm with a period that is less than 24 hours. The second frame shows the behavior of this sea hare in a light-dark cycle. The animal is clearly entrained to the 24 hour photoperiod and is day active. The last frame shows the 25 day average and periodogram to indicate the stability of such a preparation. The parieto-visceral ganglion is clearly not essential for either entrainment or the expression of the free-running circadian rhythm. Such experiments, however, do not exclude the possibility that the presence of the ganglion contributes something to the circadian locomotor rhythm.

Cellular organization of and the circadian rhythm in the eyes of Aplysia. The sea hare has two small (approximately 1 mm in diameter) eyes located just at the base and anterior to the two rhinophores which are feelers located bilaterally on the head of the animal. The eyes were first studied by Jacklet (1969b) while in our laboratory. The eye is of the closed vesicle type containing a small lens. Histological sections reveal a layer of primary photoreceptor cells with microvillus processes which extend into the space surrounding the lens. Electron microscopic studies (Jacklet, Alvarez and Bernstein, 1972) show that the receptor cells are surrounded by pigmented support cells. The primary photoreceptor is unusual in that it contains in its cell body a dense packing of clear vesicles approximately 400 Å in diameter (cf. Helix - Eakin and Brandenburger, 1967; Hermissenda - Eakin et al., 1967). Below the layer of photoreceptors and support cells is a more diffusely organized layer of secondary neuronal cell bodies, and the processes of these and receptor cells. The optic nerve, at the base of the eye, runs to the cerebral ganglion. Sener, Alvarez and strumwasser (in preparation) find that at the base of the eye there is a particularly thick neuropile.

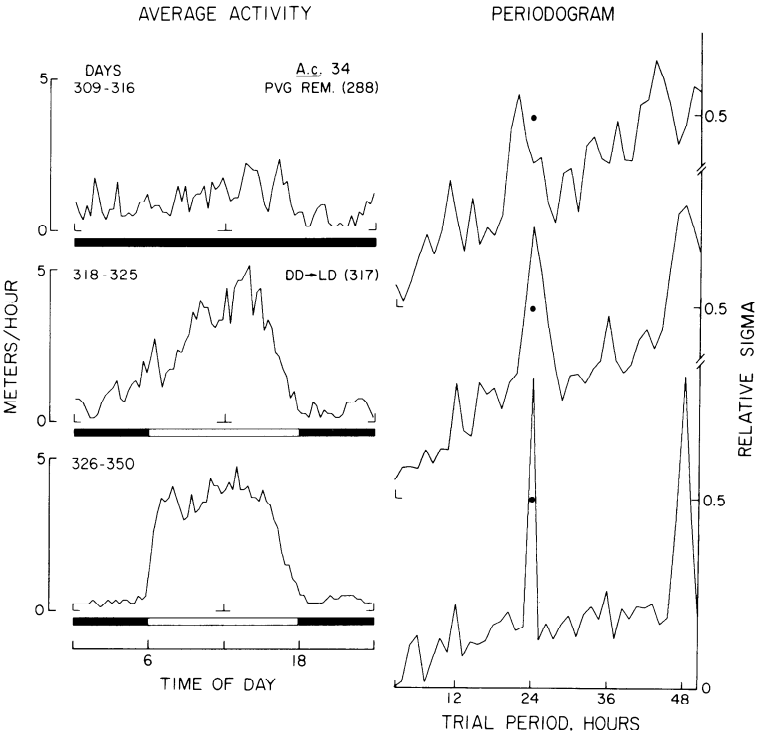

Fig.4. The average locomotor activity and periodogram analysis of a sea hare whose parieto-visceral (or abdominal) ganglion had been removed. Note that the first data frame was a run in constant darkness (red fluorescent lights on continuously at about 60 lux when measured from a view of the entire tank). Entrainment to a photoperiod (390 lux) is shown on the next two frames. (See Figure 1 for further details.)

Jacklet (1969b) showed that the normal mode of communication by the eye was a compound action potential which propagated toward the cerebral ganglion. Jacklet (1969a) found that the frequency of these compound action potentials (CAPs) in constant darkness fluctuated with a large amplitude circadian rhythm. The first cycle of this circadian rhythm of optic nerve impulses correlated well with the previous photoperiod to which the intact animal had been exposed. Activity in the eye anticipated the projected light onset and declined before the projected light offset. The eye was quiet during projected darkness. Jacklet (1969b) also found that the eye was responsive to light, exhibiting a transient fast discharge of the CAP followed by a sustained tonic discharge which was essentially an acceleration of the dark discharge as

long as the light was maintained on. Because the CAPs were graded during the transient light-on response and because the CAPs could be broken down into much smaller units by hypoosmotic sea water, Jacklet concluded that the compound action potential was possibly due to the simultaneous discharge of many neurons with emergent axons in the optic nerve.

More recent experiments in my laboratory by Audesirk (1971, 1973) utilizing agents which are known to separately block chemical and electrical synaptic transmission, allow the proposal of a simplified model of organization and connections in the eye of Aplysia. Figure 5 illustrates a diagram of this model. The photoreceptors are shown arranged radially around the lens. The second order cells are shown immediately below the photoreceptor layer. Because high magnesium-low calcium solutions or a small amount of lanthanum salt added to the normal artificial sea water will block the dark discharge and the tonic response to maintained light, Audesirk concludes that the dark discharge is due to a specialized pacemaker cell that chemically synapses with the second order neuronal population. In high magnesium-low calcium solutions (or by adding lanthanum) the chemical synapse between the pacemaker neuron and the second order cells is blocked, thus giving rise to the absence of discharge in sustained darkness and the absence of a tonic response in the presence of light.

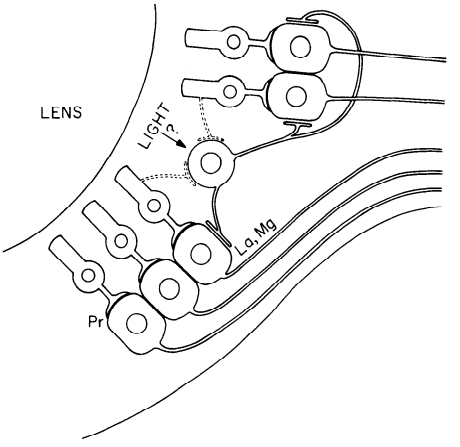

Fig.5. A model of the neuronal and synaptic organization within the eye of the sea hare. This model is based on electrophysiological and ion substitution experiments done by Audesirk (1973). The photoreceptors are the elements arranged radially closest to the lens. These cells make electrical synapses with the second order neurons whose axons project into the optic nerve. The second order neurons also make electrical junctions with one another. A single case is shown of a third type of neuron, a pacemaker cell, which makes a chemical synapse with second order neurons. The electrical synapses are blocked by propionate while the chemical synapses are blocked by high magnesium-low calcium or lanthanum ions. The tonic response to light (see text) is thought to be due either to the fact that there are chemical synapses between receptor cells and the pacemaker neuron or that the pacemaker neuron is itself responsive to light. (Modified from Audesirk, 1973.)

Figure 6 shows the nature of the compound action potential discharge in constant darkness, the typical transient and tonic discharge due to sustained light and the effects of lanthanum chloride at 1.1 mM concentration. Shortly after the addition of lanthanum chloride toward the end of line 2 the dark discharge is blocked. Also, as shown on line 3 the tonic but not the phasic component of the response to sustained light is blocked. Sometime after two rinses with artificial sea water the dark discharge eventually returns as on the last lines of this figure.

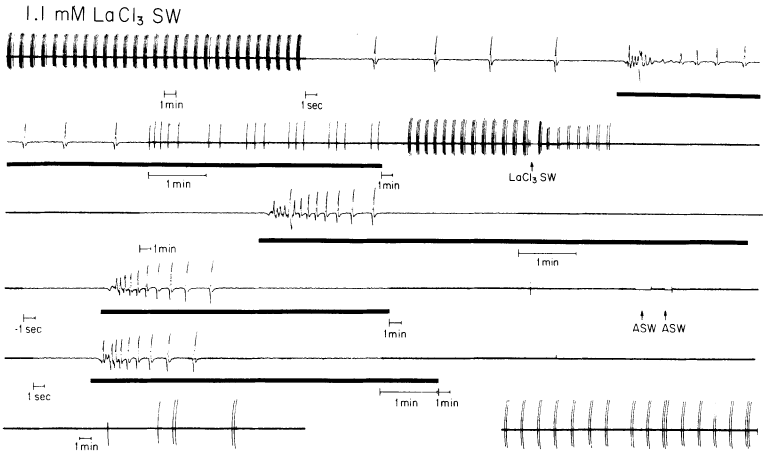

Fig.6. The influence of lanthanum chloride sea water on the dark discharge and the tonic component of the light evoked discharge in the eye of Aplysia. The eye is initially in ASW. The first four lines are consecutive recordings; line five follows with a delay of approximately 1 hour, line 6 follows with a delay of approximately 1.5 hours and the gap in line 6 represents approximately 1 hour. The total time to recovery of normal bursting patterns in the dark, after lanthanum chloride, is 3.5 hours in artificial sea water. Sustained illumination is signaled by a thick dark line immediately underneath the cell recording. Changes in paper speed are indicated by a time marker which starts with a long vertical bar and terminates with a shorter vertical bar. SW stands for sea water and ASW for artificial sea water. The spikes in this figure are the compound action potentials that are recorded from the optic nerve of the isolated eye. (From Audesirk, 1973.)

The model in Figure 5 also shows that photoreceptors are electrically coupled to the second order neurons and that the second order neurons are electrically coupled to each other. The evidence that the photoreceptors are electrically coupled to second order neurons stems from the fact that propionate substituted for chloride will totally block all components of the light response as seen in the optic nerve. However, the ERG is unimpaired, strongly suggesting that transmission between the receptors and the second order neurons have been blocked. Since high magnesium-low calcium solutions or the addition of lanthanum does not block this junction, while propionate does, Audesirk

suggests that the coupling between photoreceptors and secondary cells is electrical. Asada, Bennett and Pappas (1971) have found that propionate substituted for chloride blocks the electrotonic junctions in the lateral septate axons of the crayfish. The evidence that the second order neurons are themselves coupled is suggested by the very fact that the discharges in the optic nerve in normal solutions or those containing lanthanum are compound action potentials.

Audesirk's model of the eye already suggests that the circadian rhythm of dark discharge might emanate from the hypothetical pacemaker cell or cells. It should be emphasized that this model can only account at present for the gross features of the responses of the eye to light and the dark discharge. Intracellular recordings by Jacklet (1969b) demonstrated greater complexity in the eye than this model is able to account for. However, at present it is not thought that the additional features that Jacklet observed, e.g. inhibition of certain neurons upon light presentation, are particularly relevant toward an understanding of the circadian discharge in this eye.

Manipulation of the Circadian Rhythm in the Isolated Eye

There are four methods that have been used to manipulate the circadian rhythm of the isolated eye - light, tissue reduction, high external potassium and inhibitors of macromolecular metabolism. Eskin (1971) showed that isolated eyes could be entrained to light-dark cycles in vitro. Entrainment to 180° phase shifted light-dark cycles in vitro took three to five days whereas in vivo entrainment could be obtained in one day.

Jacklet and Geronimo (1971) removed eye tissue and claimed that if less than 0.2 of an eye had been left, after trimming, that the circadian rhythm could not be recorded. Sener (1972) has repeated these experiments trimming the eyes after a preliminary period of control recording and during projected darkness, whereas Jacklet and Geronimo had trimmed their eyes at the beginning of the experiment. Sener's results are nicely summarized in Figure 7. Thirteen pairs of eyes were used in these experiments, one for control recordings while the other eye was trimmed down to a very small piece. The average frequency of discharge of the 13 control eyes are compared with a similar average for the 13 trimmed eyes. Both curves show the typical circadian rhythm. The only difference between the two sets of eyes is that the intact eyes have a slightly higher minimum and maximum frequency of discharge; the times of onset and offset of the circadian rhythm are clearly not different between these two sets of eyes. The control eyes had a peak with respect to projected dawn at -1.4 ± 1.1 hours, whereas the experimental eyes possessed a peak at -1.5 ± 1.9 hours.

Sener estimates from light microscopy that under 50 receptor cells and perhaps less than this number of second order neurons are left in such fragments. Jacklet and Geronimo had used their results - the disturbance or absence of a circadian rhythm - to suggest that coupling between many cells each possessing ultradian rhythms were involved in the production of a circadian rhythm. Sener's results reopen the

possibility that the circadian rhythm is produced by only a few cells and suggest that Jacklet and Geronimo's results might have been due to injury of some key neurons in the base of the eye.

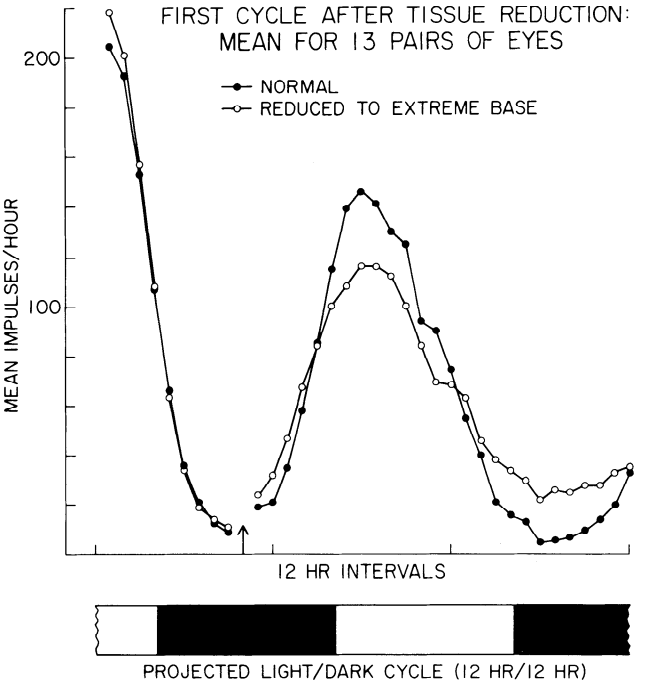

Fig.7. Comparison of the first cycle of the circadian rhythm in a group of reduced eyes and intact eyes. There were 13 eyes in each experiment. Points on the curves are hourly averages. The arrow indicates the time that both groups of eyes were exposed to illumination during which time the experimental eyes were reduced to the extreme base (remainder of eye estimated as less than 0.2 of its normal size). The projected light/dark cycle is the photoperiod that the intact Aplysia had been exposed to. (From Sener, unpublished; see Sener, 1972.)

A third way of manipulating the circadian rhythm in the isolated eye is to depolarize all of the cells of the eye with a high potassium pulse (100 mM) and to assay the shift of the rhythm with respect to a control eye. Eskin (1972) who performed these experiments in my laboratory found that the effects of a pulse of high potassium depended on the time in the circadian cycle at which the pulse was delivered.

No effects on the subsequent phase of the circadian rhythm with respect to a control eye were found if the pulse was delivered a few hours before dawn. However, a little later, around dawn, a similar pulse gave rise to a large phase advance. Pulses delivered in the late

projected night gave rise to large phase delays. A summary of Eskin's results is shown in Figure 8. The ordinate plots the amount of phase shift with advances plotted below the zero line and delays above it. Time on the abscissa is referenced with respect to the projected light cycle. It should be noted that there are two regions where potassium has minimal or no effect. Four hour pulses that start approximately 4 hours prior to light onset, as well as 4 hour pulses applied near the end of the light period have little or no effect. The fact that there are two zero effect zones spaced about 12 hours apart and the fact that 9 hours of delay could be obtained for a 4 hour pulse at a particular phase point in the cycle are strong evidence that the clock was not merely stopped during the high potassium pulse. The mechanisms, however, by which membrane depolarization might couple to and influence the presumably intracellular circadian system are unknown.

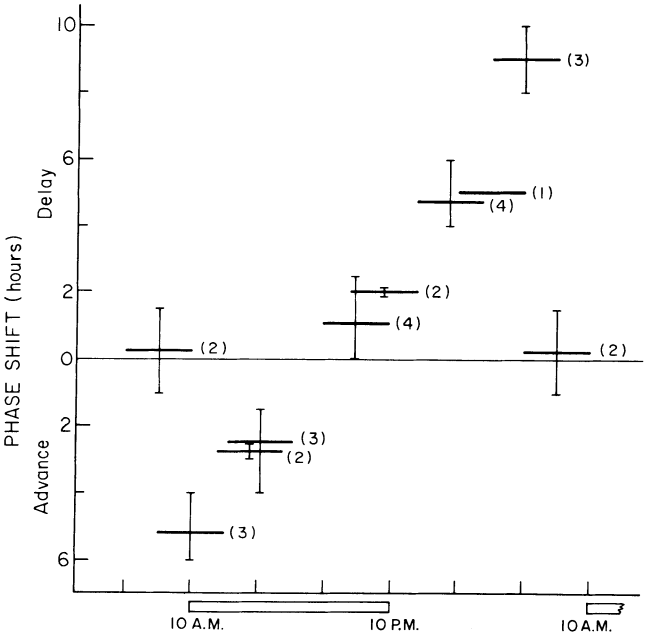

Fig.8. Phase shift of the circadian rhythm of the isolated eye of Aplysia induced by 4 hour pulses of high potassium (100 mM) as a function of the time in the cycle at which the high potassium treatment occurred. The horizontal bar delimits the duration of the high potassium pulse. The vertical bar is the range of phase shift obtained in the eyes whose number is given in parentheses. The phase shift of the experimental eye is always referred to the position of the peak of the circadian rhythm with respect to the control eye which is run at the same time. The projected light cycle is shown below the abscissa, the rectangle indicating lights on. (From Eskin, 1972.)

A fourth method of manipulating the eye suggests that a certain pattern of RNA and protein synthesis may be necessary for maintaining the rhythm. Rothman has performed experiments in which a 3 hour pulse of aflatoxin B1, a reversible inhibitor of RNA synthesis, has differential effects on the rhythm depending on the time at which it is administered (Rothman and Strumwasser, 1973). Figure 9 compares 5 control eyes with 5 experimental eyes. The control eyes have a clear circadian rhythm of optic nerve impulse discharge. The experimental eyes were allowed to cycle once and a pulse of aflatoxin B1 was delivered during the late projected afternoon and the early projected night. The experimental eyes turn on late for the next cycle, reach about one fifth the amplitude of the control eyes for the second cycle and are no longer rhythmic in that the optic nerve impulses do not turn off. The rhythm, if at all present, is clearly abnormal. Rothman finds that similar aflatoxin pulses delivered 180° out of phase (that is, in the late projected night and into the early projected day) have virtually no effects on the subsequent cycle of the experimental eyes. The differential sensitivity of the eyes to aflatoxin pulses given at different times in the circadian cycle suggests that the control for the circadian cycle may involve particular species of RNA and protein that are synthesized at some particular temporal phase point.

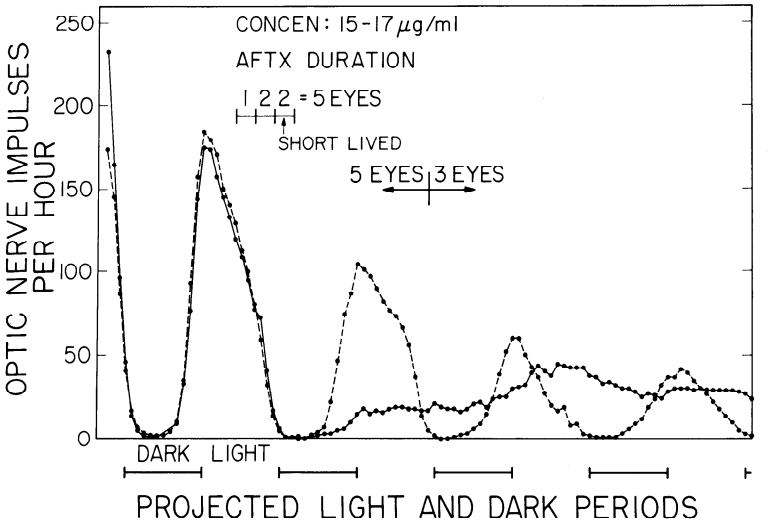

Fig.9. The effects of Aflatoxin B1, administered for 3 hours, on the circadian rhythm of optic nerve impulses in the eye of Aplysia. The two curves were generated by taking hourly averages of the optic nerve impulses from a set of 5 control (dashed curve) and 5 experimental (solid curve) eyes. "Projected light and dark" refers to the photoperiod that the intact Aplysia had been exposed to. Aflatoxin (AFTX) 3 hour pulses ranged from about 6 hours prior to projected dusk to 3 hours after dusk. (From Rothman, unpublished; see Rothman and Strumwasser, 1973.)

Circadian Rhythms in Particular Neurons of the Parieto-Visceral Ganglion

The eyes of the sea hare have a circadian rhythm of optic nerve impulses as has just been discussed. There are also neurons in the parieto-visceral ganglion (PVG) of the sea hare that possess circadian oscillators. The eye has the disadvantage that up to now the circadian rhythm can only be recorded from the optic nerve over extended periods of time and not from individual cells within the eye. The PVG offers the advantage that at least one identifiable neuron in it is known to possess a circadian oscillator and can be recorded from intracellularly for several days. One of the factors contributing to the entrainment of the circadian rhythm in the parabolic burster or R15 neuron is photoperiod. A number of papers have described the circadian rhythm in this neuron in the isolated ganglion (Strumwasser, 1965, 1967a; Lickey, 1969). In this section, I will describe recent results in which nerve trunk recordings from the organ cultured PVG (Strumwasser and Bahr, 1966) have been obtained for periods up to six weeks (Strumwasser, 1967b, 1971). These recordings have allowed us to verify that there are other neurons in the ganglion with a similar circadian rhythm which can be expressed under organ culture conditions. The location, however, of the cell bodies of these neurons in the ganglion is not presently known.

The PVG can be organ cultured in Eagle's minimum essential medium made up in filtered sea water containing 20% Aplysia serum for periods up to six weeks (Strumwasser and Bahr, 1966; Strumwasser, 1971). During the first four to five of these six weeks, the resting and action potentials of the neurons appear normal as well as the spontaneous or evoked postsynaptic potentials. The ganglion can be mounted in a special sterilizable chamber in which the nerve trunks are pulled through miniature tunnels containing a pair of recording platinum-iridium wires. Spontaneous unitary axon spikes can then be observed in the recordings (Strumwasser, 1967b, 1971). These spontaneous unitary spikes depend, for their maintained discharge, on connection with the ganglion. The presence of unitary spikes in a recording from a nerve trunk is usually associated with the presence of several large axons among the population of axons in the nerve trunk. It has been shown previously that stable unit recordings can be obtained from such preparations for up to six weeks (see Figures 13 and 14 in Strumwasser, 1971).

The major problem with such recordings has been to sort the units out by some automatic technique. In my laboratory special hardware has been constructed in association with a digital computer that allows the reliable sorting of up to eight different axonal discharges from a single nerve trunk. The sorting is done on-line and will not be described here. Figure 10 shows the waveforms of two small units in the genital nerve between days 12 and 17 of an organ cultured PVG. The waveforms shown were classified by the on-line sorter in a highly reliable way. The waveforms are also found to be quite stable from day to day. Slow changes that normally occur in the waveforms are easily accommodated by an operator changing some of the parameters on which sorting is based.

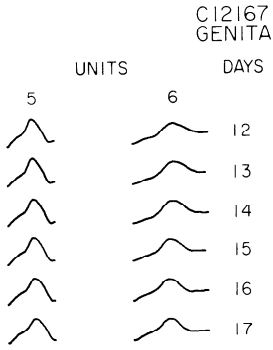

Fig.10. Waveforms of two axonal units in the genital nerve of the organ-cultured parieto-visceral ganglion of Aplysia. The waveforms shown were sorted on-line by a digital pattern recognizing device operating in conjunction with a digital computer. Each waveform is an average of several waveforms sampled at 3 hour intervals throughout each day for a 10 minute period.

Periodogram analysis of days 12 to 17 are shown for three units in the genital nerve of this same preparation in Figure 11. It can be seen that two of the three units (unit 0 and unit 5) have circadian rhythms whereas unit 6 does not appear to have any, at least over this period.

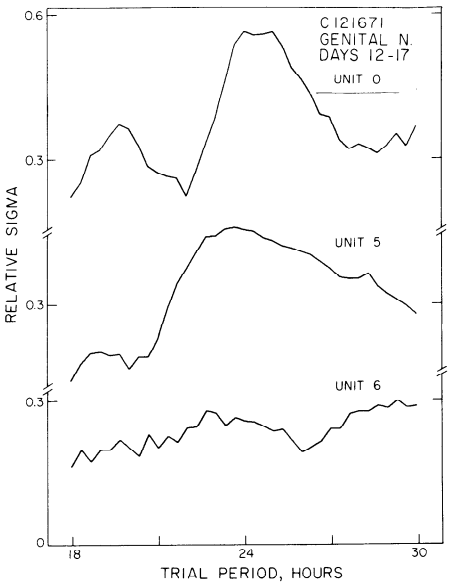

Fig.11. Periodogram analysis of 3 simultaneously-recorded axonal units in the genital nerve of the organ-cultured parieto-visceral ganglion. The waveforms of units 5 and 6 are shown in Figure 10. For further details on periodograms, see Figure 1 and associated text.

Furthermore, it is interesting that unit 5 and unit 0 have peaks in the periodogram that are separated by about one hour. Inspection of the smoothed frequency of firing curves of these two units, as a function of time, clearly reveals that the waveforms of the circadian rhythms and the phases of the peaks are not synchronous between these two units and that there is relative motion between the two units, with respect to time. These facts indicate, most probably, that these two neurons are free running with slightly different periods. If these two units are coupled, the coupling must indeed be weak. The presence of circadian rhythms within individual neurons in the PVG in organ culture suggests that the eyes of Aplysia do not drive these oscillators but rather probably entrain them.

Pharmacological Isolation of a Neurosecretory Neuron with a Circadian Rhythm

The parabolic burster of the PVG is a neurosecretory neuron with a circadian rhythm of impulse activity which is expressed in the isolated ganglion. Early studies were based on prolonged intracellular recordings (about 2 days) from this neuron in the isolated ganglion (Strumwasser, 1965, 1967a, b; Lickey, 1969). These studies showed that the peak activity in the parabolic burster occurred usually around projected dawn of the light-dark cycle that had been administered to the intact organism, this phase angle being similar to that of the circadian rhythm in the isolated eye. Some parabolic bursters, however, showed major peaks at projected dusk (Strumwasser, 1967a); Lickey (1969; Lickey et al., 1971) has presented evidence that there is a seasonal influence on the phase angle of the parabolic burster with respect to the entraining photoperiod.

More recent studies have been aimed at investigating whether impulse activity is a requisite for the production of a circadian rhythm. A calcium-free artificial sea water and the addition of tetrodotoxin (TTX) abolishes all the impulse activity in the ganglion as evidenced by extracellular recording from the nerve trunks and intracellular recording from several cell bodies in the ganglion. There are no recordable intracellular post synaptic potentials under such conditions. The only electrical activity that can be obtained under such conditions is that of slow membrane oscillations in the pacemaker cells; the nonpacemaker cells of the ganglion, such as the giant cell, R2, never show such membrane oscillations (Strumwasser, 1968, 1971; Strumwasser and Kim, 1969). The frequencies of these membrane oscillations agree well with the burst rate in the bursting pacemakers such as R15 just before pharmacological isolation. At least one full cycle of a circadian rhythm can be expressed in the parabolic burster in the absence of synaptic input and the inability to produce impulses.

Figure 12 illustrates the effects of pharmacologically isolating the parabolic burster about one hour after projected dusk. Each line in this record is one hour long. The endogenous oscillations are present for approximately 12 hours, terminating shortly after projected dawn; the subsequent 10 hours of recordings demonstrate that the parabolic burster is inactive. A convenient physiological test that can be per-

formed during this period, to make sure that the cell is not dead, is to apply a small depolarizing pulse which at the termination of the current causes a long lasting hyperpolarization (Strumwasser, 1968). Two examples are shown at "test" (lines 18 and 21). In addition, the pharmacological aspects of TTX and the calcium-free medium are completely reversible when the chamber is perfused with filtered sea water. Both spike generating mechanisms and postsynaptic potentials return and are elicitable from cells in the ganglion, including the parabolic burster.

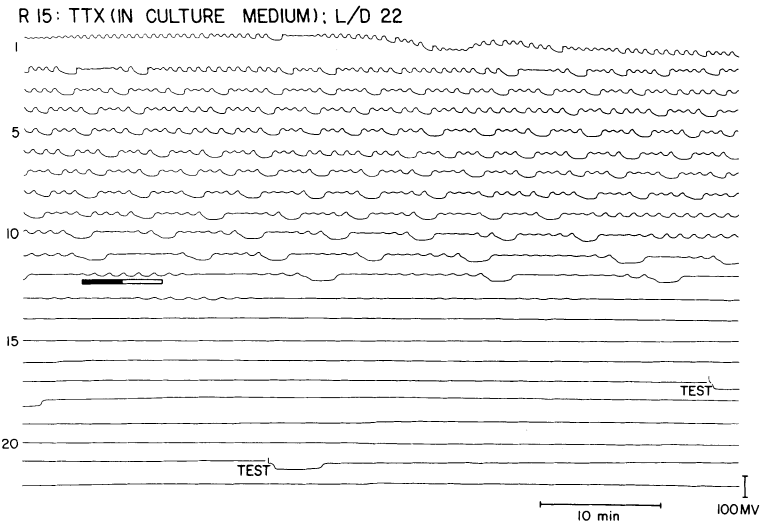

Fig.12. Long-term intracellular recording from the parabolic burster neuron (R15). The impulses in the PVG were blocked by tetrodotoxin (TTX, 25 µgm/ml). The PVG was maintained in culture medium rather than filtered sea water (Strumwasser and Bahr, 1966). Each line of recording represents one hour. The PVG was obtained from an Aplysia entrained to 22 light/dark cycles, the projected dawn transition occurring on line 12. At "test" (lines 17 and 21), about 3 x 10^{-9} A of depolarizing current was passed across the cell membrane for about 15 seconds resulting after current flow, in a long-lasting hyperpolarizing response (referred to as a POBH, Strumwasser, 1968). Temperature was 14°C.

TTX, however, has a phase shifting effect on the circadian rhythm that is not presently understood. As can be noticed from Figure 12, the cell is oscillating during projected night and quiet during projected day. The 180° phase inverting effect of TTX can be induced at other times than around projected dusk, as can be seen from Figure 13. In this example, TTX was applied approximately five hours prior to projected dusk; the parabolic burster remained quiet during the last five hours of projected day and became active at projected dusk. In this experiment, activity terminated approximately 3.5 hours prior to projected dawn. These experiments indicate that impulse production and synaptic transmission are not required within the ganglion for at least the expression of one cycle of the circadian rhythm in the parabolic

burster. More subtle methods of pharmacological isolation and/or recording perhaps are needed in order to allow the parabolic burster to express more than one cycle of its circadian rhythm when impulses and synaptic transmission are blocked in the ganglion. The phase shifting properties of TTX may be due to the small but sustained depolarization that occurs in the presence of this agent. In the parabolic burster TTX causes a 5-10 millivolt depolarization along with its blocking effects on impulses. The speculation that this depolarization is the cause of the phase shift is reasonable in view of the demonstration by Eskin (1972) that potassium-induced depolarization in the eye of Aplysia causes predictable phase shifts in the circadian rhythm of that preparation.

Mechanisms of "Slow" Pacemaker Oscillations

In the preceding section it was demonstrated that the circadian rhythm (CR) in the parabolic burster is expressed through oscillations of the membrane potential. These oscillations are here termed "slow" pacemaker oscillations to distinguish them from the pacemaker potentials that occur between spikes during repetitive firing. There are good arguments for believing that insight into these slow pacemaker oscillations will reveal useful information concerning the circadian mechanism (CRM). The CRM must couple to the neuronal membrane if it is to be expressed as a pattern of impulses and the slow pacemaker oscillations serve as the intermediary mechanism between the CRM and the pattern of impulses generated. This coupling is an output coupling of the CRM to the membrane. An input coupling of the membrane to the CRM also exists. This input coupling presumably mediates entrainment and the best evidence for this in Aplysia comes from the studies of Eskin (1972) on the effects of depolarization, induced by high potassium on the CR of the eyes of Aplysia.

Insights into the output coupling mechanism may be expected when there is more complete knowledge about the nature of the membrane mechanisms involved in slow pacemaker oscillations. The CRM presumably couples to one or more of the membrane mechanisms controlling slow pacemaker oscillations in order to express its output.

There are four important facts concerning the slow pacemaker oscillation in the parabolic burster. First, there is a special sodium channel utilized by the slow pacemaker mechanism, independent of the electrically-excitable sodium channel used by the action potential mechanism. The evidence for this consists of the fact that slow pacemaker oscillations continue when the electrically excitable sodium channel is blocked by TTX (see Figures 11 and 12). However, these slow oscillations are sodium-sensitive for when either choline or Tris is substituted for sodium, the oscillations stop (Strumwasser, 1968; Strumwasser and Kim, 1969).

The second important fact about the pacemaker mechanism is that in the parabolic burster about one-half of the total membrane conductance is sodium-dependent. Figure 14 compares the membrane resistance of a pacemaker neuron (the parabolic burster, R15) and a non-pacemaker neuron (the giant cell, R2) when in filtered sea water and

after substitution of choline for sodium. There is a drastic change in membrane resistance in the parabolic burster (an increase of about 100%) while R2 shows little resistance change (less than 5%). This two-fold membrane resistance increase in the parabolic burster, in choline or Tris substituted for sodium, implies that the resting membrane has a sodium leak that is one-half the total membrane conductance. In view of the fact that the non-pacemaker neuron, R2, does not possess this high leakage to sodium, this latter parameter may be uniquely built into the pacemaker membrane and a necessary requirement for sustained slow oscillations.

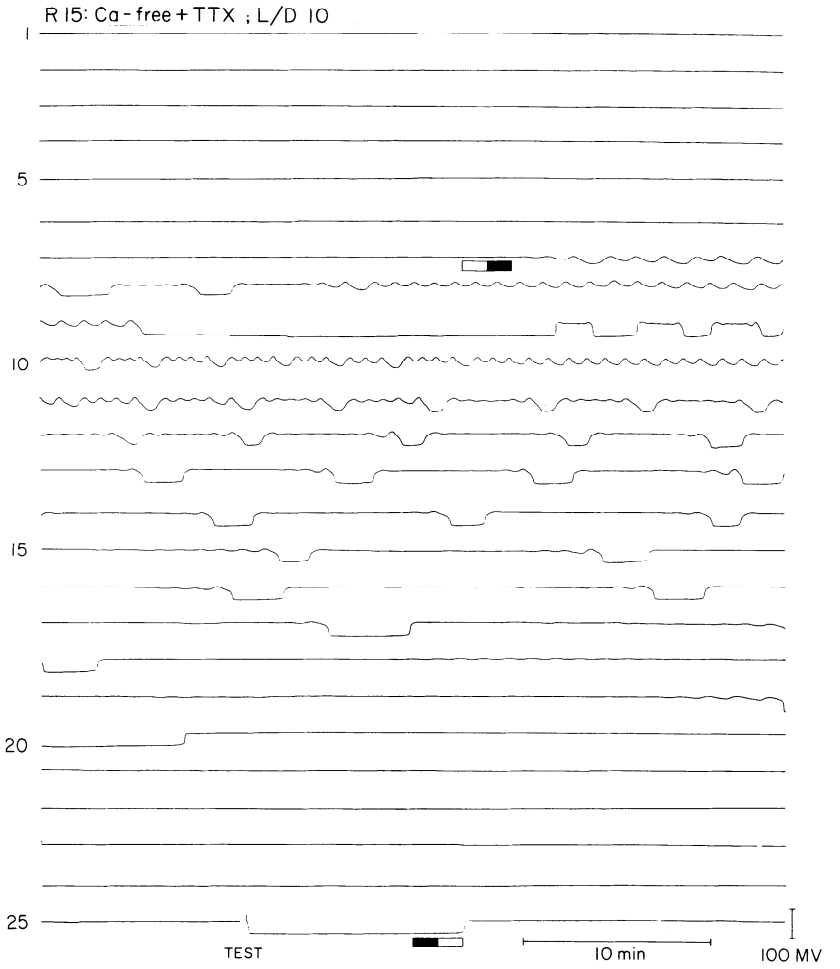

Fig.13. Long-term intracellular recording from the parabolic burster neuron (R15). The impulses in the PVG were blocked by tetrodotoxin (TTX, 25 µgm/ml) and synaptic transmission by calcium-free artificial sea water. Each line of recording represents 40 minutes. The PVG was obtained from an Aplysia entrained to 10 light/dark cycles, the projected dusk transition occurring on line 7. A short depolarizing current was passed across the membrane at "test" (see Figure 12). Temperature was 14°C. (From Strumwasser, 1971.)

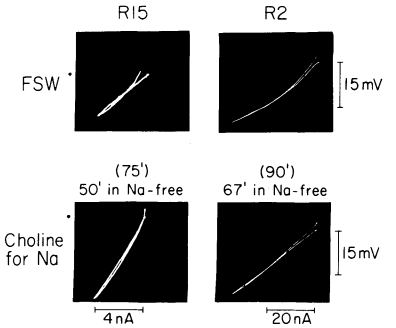

Fig.14. Comparison of the membrane resistance changes of R15 and R2 in filtered sea water (FSW) and after substitution of choline for sodium. A slowly rising and falling "sawtooth" of hyperpolarizing current was passed across the cell membrane with one electrode while a second intracellular electrode measured the membrane potential changes. Voltage is on the ordinate and current is on the abscissa. The filled circle to left of each frame is positioned to indicate the resting potential for the left hand frames; the resting potential for the right hand frames are indicated by the tops of the voltage calibration bars. nA stands for 10^{-9} A. Electrode current was measured by an operational amplifier connected to the virtual ground in the bath.

Thirdly, the pacemaker oscillations are very sensitive to interference with active transport of sodium across the membrane. A particularly convincing way to demonstrate this fact is to use the substitution of lithium for sodium. Lithium is presumably not recognized by the membrane ATPase involved in sodium transport (Flynn and Maizels, 1949; Ritchie and Straub, 1957; Keynes and Swan, 1959), but will generally substitute for sodium, at least in the electrically-excitable sodium channel supporting the action potential. Figure 15 shows the effect of lithium substituted for sodium on the parabolic burster slow pacemaker oscillations. Perfusion of lithium for sodium starts and is completed on line A. Within 3 minutes after completion of the perfusion, slow pacemaker oscillations have stopped (line B). Immediate hyperpolarization of the neuron (middle of line B, solid marker line) is unable to restore slow pacemaker oscillations. Even stronger hyperpolarization a few minutes later (line C) does not restore slow pacemaker oscillations. The effects of lithium substituted for sodium are completely reversible as is shown in lines D, E and F. It should be noted in this experiment, which is typical, that spontaneous burst production did not occur until 1.5 hours after returning to filtered sea water from Li for Na sea water. Once the slow pacemaker mechanism generating bursts of impulses recovered, however, it was essentially normal when continuously monitored over the next 12 hours (see line F).

A fourth important fact concerning the pacemaker mechanism in the parabolic burster is its dependence on a normal external chloride concentration. Other bursting pacemakers in the same ganglion do not have this chloride sensitivity as demonstrated in Figure 16. This figure demonstrates a simultaneous intracellular recording from L3 (Frazier et al., 1967) and the parabolic burster (R15). When acetate is substituted for chloride (lines 2 and 3) the parabolic burster stops

its oscillations within the first perfusion while the L3 neuron, although modified in the waveshape of the slow pacemaker oscillation, continues to oscillate even 10 hours later (see line 6). Quite typically the parabolic burster never fires during the substitution of acetate for chloride although, in a few experiments, slow repetitive firing has occurred for a short time after several hours of substitution.

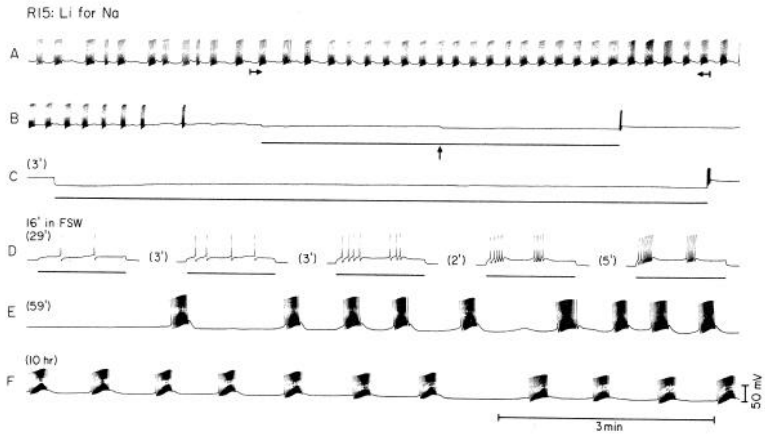

Fig.15. Abolition of slow pacemaker oscillations by lithium substituted for sodium. In line A 50 cc of lithium for sodium artificial sea water were perfused through an 8 ml chamber containing the PVG between the arrows. In line B after pacemaker oscillations had stopped, continuous hyperpolarization was applied as indicated by the heavier marker line; at the arrow the hyperpolarization was increased. Stronger hyperpolarization of the membrane is shown on line C. Spikes fired when hyperpolarization was released. Between lines C and D filtered sea water (FSW) was perfused through the chamber. All the spikes shown on line D were elicited by applying depolarizing currents for the duration shown by the heavier marker line. The first burst on line E is the first spontaneous burst that occurred after the pacemaker oscillations had been blocked by lithium for sodium in line B.

A model for slow pacemaker oscillations. The studies of Connor and Stevens (1971b, c) show that repetitive firing in nudibranch neurons is dependent on a specific potassium channel which is activated by stepping from potentials negative to the resting potential toward the resting potential. This process is thought to be mediated by channels operationally distinct from the K^+ channels mediating "delayed rectification." Essentially similar findings have been recently described by Neher and Lux (1971) in Helix pacemaker neurons. Connor and Stevens (1971c) show, by computation, that the first two spikes generated by a sustained DC current are properly predicted by consideration of the two conventional channels (for Na^+ and K^+) and this new potassium channel. While this special potassium channel may have relevance for the precise timing of impulses in response to a slow pacemaker

oscillation, my own view is that this channel does not contribute significantly to the actual slow pacemaker oscillations. The primary reason for this point of view is that lithium substituted for sodium abolished the slow pacemaker oscillation even in the presence of weak to strong hyperpolarization. Also, in the parabolic burster, substitution of acetate, propionate or butyrate (Strumwasser, 1968) for external chloride immediately stops slow pacemaker oscillations which again fail to occur even when the membrane is hyperpolarized. The findings of Eaton (1972) that the decline of the outward (K^+) currents in the parabolic burster with long voltage clamp pulses is probably due to an accumulation of K^+ just outside the membrane, rather than a K^+ inactivation, as in nudibranch neurons (Connor and Stevens, 1971a), is probably of significance for the increased duration of the successive action potentials during a burst (Strumwasser, 1965, 1967a; Faber and Klee, 1972).

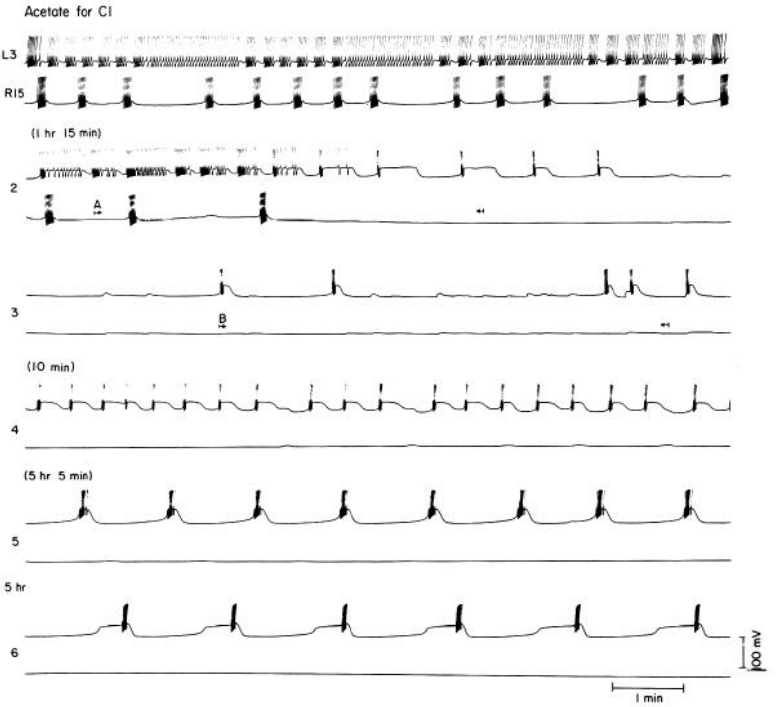

Fig.16. Abolition of pacemaker oscillations in R15 by acetate substituted for chloride. Simultaneous intracellular recording from an upper left quadrant burster (L3) and R15. In line 2 perfusion of acetate for chloride artificial sea water takes place between the arrows at A and again on line 3 between the arrows at B. The time between records on separate lines is shown in parentheses. Lines 2 and 3 are continuous.

Strumwasser and Kim (1969; Strumwasser, 1971) have suggested and computed that membrane oscillations can occur in a membrane system with a high sodium leak due to intermittent activation of a sodium electrogenic pump (in the case of the parabolic burster a sodium-chloride electrogenic pump). It should be noted that in this computation the Na^+ and K^+ channels were treated as purely passive (electrically inexcitable). Since the pacemaker oscillations in Aplysia are essentially slow, the rise and fall of a pacemaker depolarization taking about 15-30 seconds at 14°C, this intermittent pump mechanism seems reasonable on purely kinetic grounds. Connor and Stevens (1971b) report time constants of decay of the special potassium channel between 220-600 milliseconds at 5°C. Since they state that this process has a Q_{10} of approximately 3, the time constant at 14°C would be approximately 200 milliseconds at maximum. This time constant is at least 2 to 3 orders of magnitude too fast to account for the very long interburst intervals that can be seen in the parabolic burster (see Strumwasser, 1967b, Figure 18; and Figures 11 and 12 of this paper).

In conclusion, the mechanism of slow pacemaker oscillations in the parabolic burster appear to depend on the following: 1) A special sodium channel that provides a relatively constant inward depolarizing current and that is not affected by tetrodotoxin. 2) A large contribution of this channel (about 50%) to the total "resting" conductance of the cell membrane. 3) A sodium (chloride-dependent) electrogenic pump that is probably activated by the concentration of sodium at the inner membrane surface (see Thomas, 1972).

Special Biochemical Characteristics of Pacemaker Cells

By investigating the nature of proteins unique to pacemaker cells, and obtaining insights into the regulation of these molecules within the cell one may be led eventually to the nature of the coupling between the CRM and the membrane. Autoradiographic experiments had shown that H^3-leucine was incorporated into neuronal cell bodies of the parieto-visceral ganglion during 4 hour incubation periods with minimal incorporation by the surrounding glia (Strumwasser and Bahr, 1966; Strumwasser, 1967a). Neurons adjacent to one another often showed markedly different incorporation which could be due to different leucine pools or different rates of protein synthesis within these cells. These experiments were extended, in our laboratory, by Wilson (1971) who studied the patterns of proteins synthesized within single neurons dissected from the ganglia at the end of an incubation period. A similar approach has been recently described by Gainer (1972) for the neurons of the terrestrial snail, Otala. Wilson used miniature sodium dodecyl sulfate (SDS) polyacrylamide gels to separate radioactive proteins from a single soma according to molecular weight. Pacemaker cells (such as R14, R15, and L11) in the PVG synthesize an excess of proteins around 12,000 mol wt, whereas non-pacemaker cells (such as R2 and the left pleural giant neuron) synthesize little protein in this region with peaks of synthesis around 50-60,000 mol wt (Wilson, 1971; Ram, 1972).

In order to determine the functional significance of certain of the large peaks of newly synthesized proteins, Wilson and I developed the

following strategies for new experiments. We assumed that the synthesis of proteins might be regulated directly or indirectly in association with particular functions that they might subserve. For example, if one of the large peaks of newly synthesized protein were sensitive to some manipulation of pacemaker activity one might tentatively correlate this protein peak with pacemaker function. Two manipulations, one systematically giving a negative result and the other a clear positive result, will be discussed here.

Single experiments consisted of incubating one ganglion in C^{14}-leucine and another in H^3-leucine. One of these ganglia served as a control while the other was either pharmacologically treated or had certain ions in the artificial sea water substituted. One paradigm consisted of using TTX and calcium-free artificial sea water to abolish all impulses and synaptic transmission during the incubation period (see Figures 11 and 12 and associated text). Figure 17 compares a pair of R2 cells in the upper frame with a pair of R15 cells in the lower frame. No difference can be discerned between the pair of R2 cells, one of which is a control. A similar result was obtained with the R15 pair of neurons. One should notice that the R15 patterns consist of strong peaks around 12,000 and 6-9,000 mol wt. This result in Ca-free, TTX medium was not particularly surprising in R2 since this neuron produces very few spontaneous impulses and hence the change in impulse rate would be quite minimal with this pharmacological manipulation. The result was somewhat surprising for R15 however, because a change in spike production is the most dramatic influence of this pharmacological manipulation; R15 produces spiking rates over 24 hours that range from 0 to 60 spikes/minute (see Strumwasser, 1965, Figures 2-6). It should be noted however that Ca-free, TTX medium does not block pacemaker oscillations (see Figures 11 and 12).

Wilson and I used either acetate or propionate substituted for chloride to block pacemaker oscillations in R15. Utilizing a pair of doubly labeled ganglia, we found that the 6-9,000 mol wt peak was considerably reduced in R15 in the acetate or proprionate medium (Figure 18). Table 1 summarizes the results of 41 experiments on R15. Three areas of the gels have been analyzed in detail (50,000; 12,000 and 6-9,000 mol wt regions). In control parabolic bursters approximately 10% of the counts appear in the 50,000 mol wt region while 21% and 15% appear in the 12,000 and 6-9,000 mol wt regions, respectively. It can be seen that either acetate or propionate substitutions decrease the counts in the 6-9,000 molecular weight region by 80% and 72%, respectively - a statistically very significant result. This result allows us to tentatively conclude that the 6-9,000 molecular weight protein may be correlated with a pacemaker function, perhaps related to a lower rate of the sodium-chloride dependent electrogenic pump under conditions of zero external chloride media. If the absence of a chloride influx in acetate or propionate artificial sea water reduces the rate of this pump and if the 6-9,000 mol wt proteins are either components or controllers of the pump, a lower rate of synthesis of these constituents might be expected and would be meaningful.

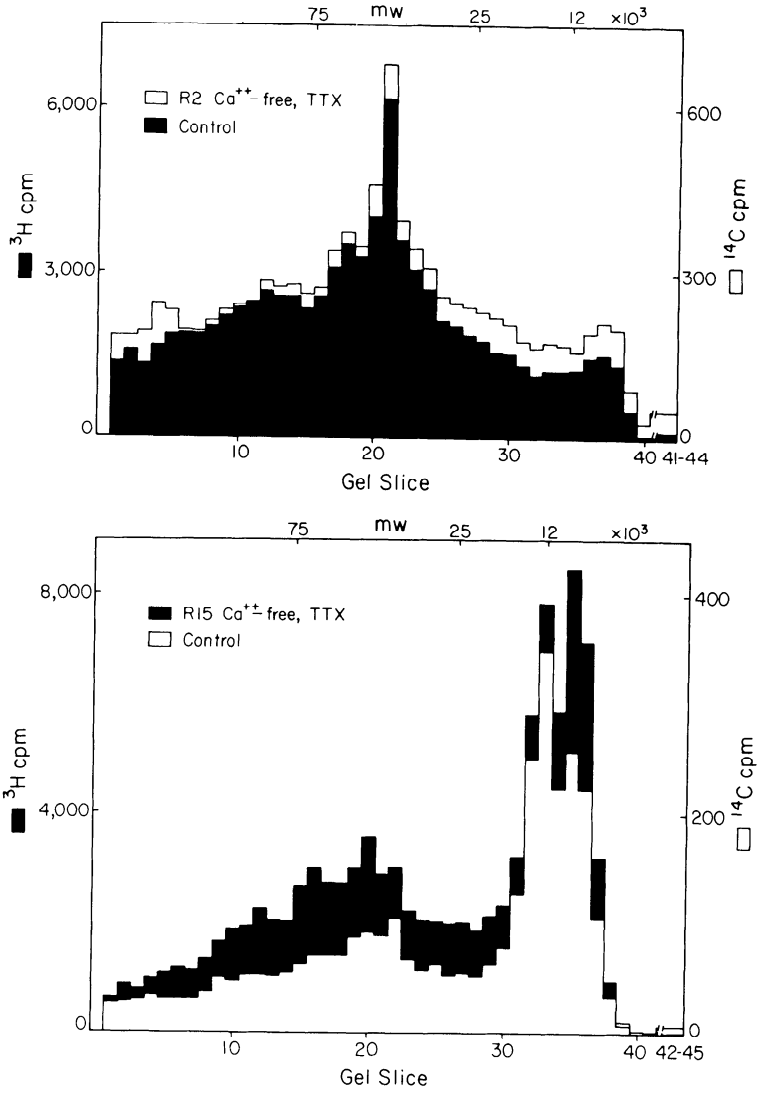

Fig. 17. Comparison of the patterns of proteins synthesized in the R2 and R15 neurons in control conditions and during pharmacological blockade of impulses and synaptic activity. Ganglia were preincubated for 4 hours without radioactive label in either control (artificial sea water) or experimental (Ca-free, TTX) solutions. One ganglion was then shifted to C^{14}-leucine (2.5 μC/ml) and the other to 4,5-H^3-leucine (100 μC/ml) media during the 12 hour incubation. The experimental incubation medium was a Ca-free,TTX containing solution. (See text for further details).(From Wilson, unpublished).

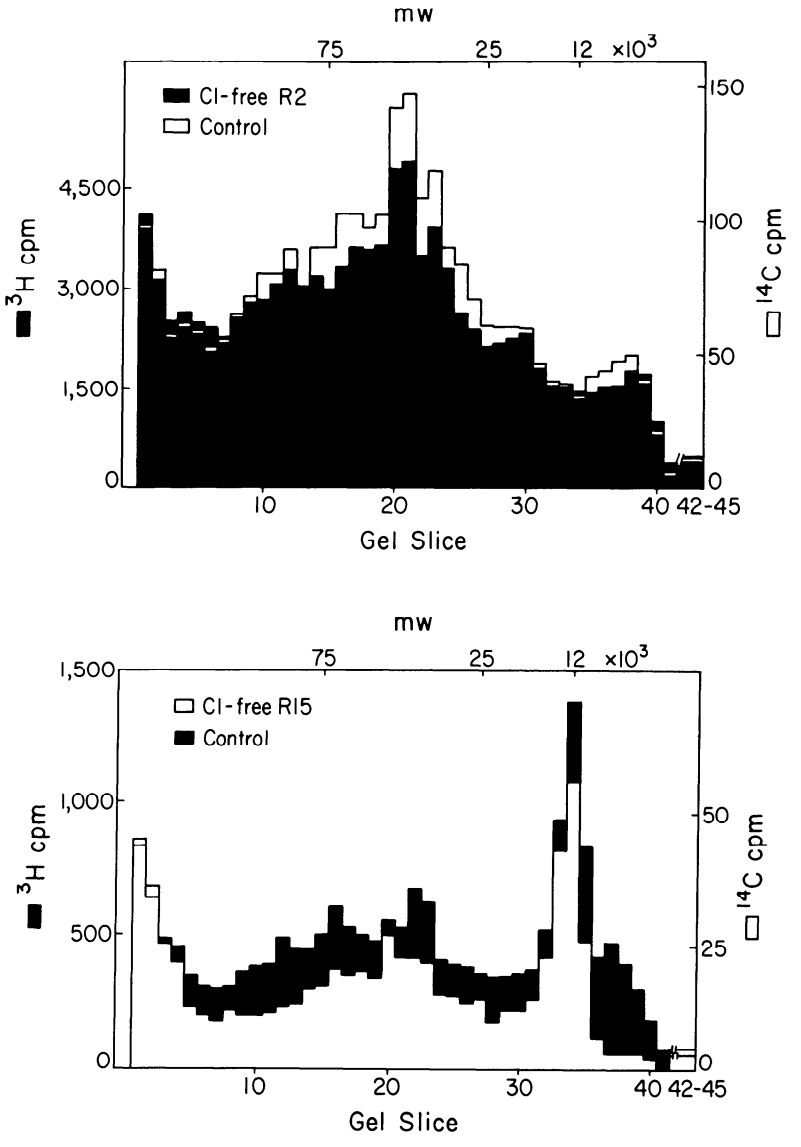

Fig.18. Comparison of the patterns of proteins synthesized in the R2 and R15 neurons in control conditions and during blockade of slow pacemaker oscillations by acetate substituted for chloride. Protocol as given in Figure 17 with experimental solution being an acetate for chloride substitution. (From Wilson, unpublished.)

TABLE 1

THE EFFECTS OF ION REPLACEMENTS ON THE PROTEIN SYNTHESIS PATTERN OF R15

(Average % cpm in gel at:)*

	50k mw	12k mw	6-9k mw	N
Control	9.8± 1.1	20.9 ± 3.7	14.7 ± 4.1	14
lo Ca^{++}, hi Mg^{++}	9.7	22.7	10.5	2
Ca^{++}-free, TTX	8.5 ± 1.1	24.2 ± 6.4	15.4 ± 1.0	3
Cl by acetate	10.0 ± 0.8	25.2 ± 4.9 ($.02 < p < .05$)	3.0 ± 0.5 ($p < .01$)	5
Cl by propionate	9.5 ± 0.7	25.2 ± 6.5	4.1 ± 0.4 ($p < .01$)	4
Na by Tris	9.0 ± 0.5	33.8 ± 5.9 ($p < .01$)	4.5 ± 0.6 ($p < .01$)	5
Na by choline	10.8	21.9	11.7	2
Na by arginine	9.4 ± 1.1	19.3 ± 3.9	19.6 ± 7.5	3
Na by lysine	10.1 ± 1.4	23.3 ± 2.0	13.7 ± 3.5	3

*Ratio of cpm in 3 gel slices at the region indicated (50k mw = 50,000 mol wt region, etc.) to total cpm in the gel times 100. Means ± standard deviations for N samples are shown.

Conclusions

It appears that both slow and even circadian oscillators can occur as special mechanisms within single neurons. In the parabolic burster neuron (and the eye) of Aplysia, the slow 1/minute and circadian oscillations already span three orders of magnitude, in terms of frequency; therefore it seems that single mechanisms governing both oscillators are unlikely. There are weakly electric fish (certain fresh water gymnotids) that generate electric pulses, used in navigation and communication, at rates around a few hundred Hz for all of their life (Lissmann, 1958). It seems unlikely that this high frequency oscillation would have a mechanism similar to that of the parabolic burster slow pacemaker oscillator which is four orders of magnitude lower in frequency. It appears likely that different aspects of cellular organization (pumps and channels in membranes, transcriptional and translational controls in macromolecular metabolism) have evolved to cover these seven orders of magnitude of frequency.

The functional significance of oscillators can only be worked out when there is enough specific information in favorable cases. The eyes of Aplysia, from the evidence presented in this paper, have a circadian

rhythm of optic nerve impulses which appears to serve to synchronize other circadian oscillators. Macrobehaviors, such as sleep, waking and cycles of sexual activity, can be imagined to be controlled by such systems of circadian oscillators, but the details clearly need to be worked out before most of us will be convinced. Some circadian oscillators are neurosecretory. The nature of neurosecretory products and their physiological and behavioral effects is an area with sparse information but again in favorable cases, such as Aplysia, a single polypeptide neurosecretory product (Toevs and Brackenbury, 1969; Toevs, 1970; Arch, 1972) is known to organize behavioral egg-laying (Kupferman, 1967; Strumwasser et al., 1969). The conservative nature of neuronal and glial mechanisms discussed in the introduction of this paper is a constant reminder that the chances of encountering general principles from special cases, where the system is more accessible to analysis, are quite good indeed.

Acknowledgements

There are individuals who have helped in many phases of the original work that are not appropriately cited in the text. I am happy to use this occasion to express my gratitude to Miss Suzy Bower, Mr. Ben Ellert, Mr. J. J. Gilliam, Mr. Kent Gordon, Miss Sandra Miali, Miss Shelly Rempel, Mr. John Rupp and Mr. Floyd Schlechte. Original research reported in this paper has been supported by grants from the NIH (NS 07071), NASA (NGR 05-002-031) and the Sloan Foundation to the author. Computer facilities have been supported by a grant from the NSF to Professor G. Ingargiola (GJ 28424).

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WORKSHOP ON ION-SELECTIVE MICROELECTRODES

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THE DECLINE IN EMPHASIS ON BASIC MEDICAL SCIENCES IN MEDICAL SCHOOL CURRICULA*

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Abstract

Medical education today is losing its science-oriented base. The gain that the public hopes to receive by increasing medical manpower will be illusory if the competence of medical graduates is reduced. The increasing importance of science to competent medical practice would argue for an opposite trend.

The last decade has witnessed a progressive upheaval in medical school curricula and objectives. The forces responsible for the counter-revolution against the Abraham Flexner (1) model of medical education are numerous and complex. It is the purpose of this communication to report on the current status of the new revolution that is taking place, to outline briefly the apparent reasons for the changes, and to suggest their implications to the public at large. A study has been made as to changes that have occurred with respect to education in the basic medical sciences with special emphasis upon the field of physiology. Informational bulletins and catalogues were obtained from 106 of the 108 medical schools operating in the year 1971-72. Questionnaires were sent to Heads of Departments of Physiology in schools having such departments to obtain information concerning hours assigned in each school to lecture, conference, demonstration, laboratory and/or programmed learning for the field of physiology, as well as information on changes in time assignment since 1961-62. In addition information was requested concerning the nature of the laboratory study, if any, in the several schools. Furthermore, other reports have been examined and their findings summarized and compared.

The total assigned hours for basic physiological instruction in the 106 medical schools for which data have been obtained for 1971-72 are given in Figure 1. There is obviously a very wide spread between the minimum and the maximum numbers of assigned hours, reflecting wide differences in the perceived importance of physiological science information on the part of curriculum makers at the several institutions. The mean number of assigned hours for the 106 institutions is 159.

For comparison with an earlier period Figure 2 presents the data obtained from 74 of the medical schools which were in operation ten years ago. The mean assignment then was 246 hours. For the same 74 schools in 1971-72 the mean was 170 hours. Figure 3 shows the

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*This study was supported by the Louis W. and Maud Hill Family Foundation. The substance of the report was presented to the Association of Chairmen of Departments of Physiology in conjunction with the meetings of the Association of American Medical Colleges on November 5, 1972.

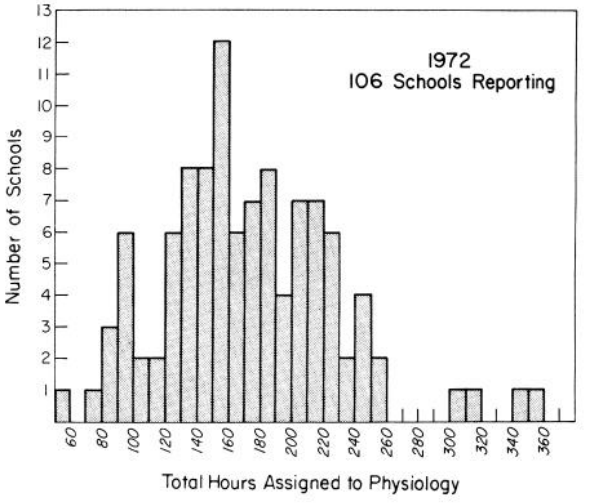

Fig.1. Numbers of hours assigned to instruction in physiology in U.S. medical schools for the academic year 1971-72.

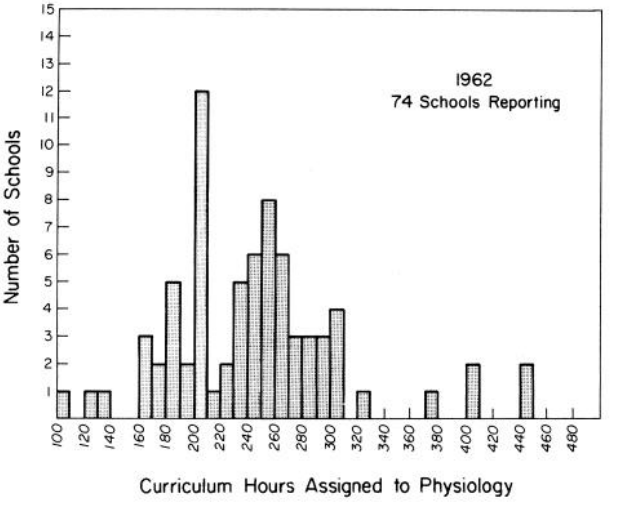

Fig.2. Numbers of hours assigned to instruction in physiology in the schools providing information for the academic year 1961-62.

changes in number of assigned hours between 1961-62 and 1971-72. It will be noted that no reporting institution has increased its assigned hours. The maximum decrease for any school was 70 per cent and the average decrease was 31 per cent. There has been a large increase in numbers of medical schools in the last decade, and in most of the newer schools the assignment of hours to the basic medical sciences is low. In addition in some institutions major cuts had been made before 1961-62. Consequently the data in Figure 3 underestimate the recent decline in emphasis.

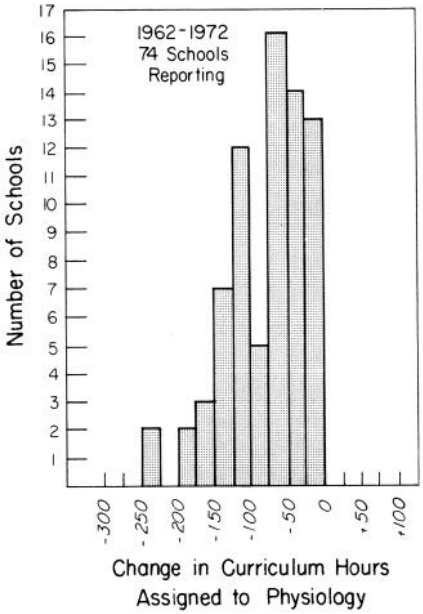

Fig.3. Distribution among medical schools reporting changes in number of curriculum hours assigned to physiology between 1962 and 1972.

As regards current tendencies in education practices the data in Figure 4 are perhaps the most interesting. It will be noted that there are now ten medical schools in which regularly assigned student laboratory work in physiology has been entirely abandoned. Data assembled by Aviado (2) show that in 25 per cent of medical schools there is no assigned time for laboratory instruction in pharmacology. Furthermore there are many institutions in which laboratory instruction occupies a very small number of hours.

Questions were also asked as to the amount of opportunity medical students had to participate in experiments using living animals. In 15 schools there were no assigned experiments on any living animal. The data obtained with respect to studies employing dogs are shown in Figure 5. The median number for student use of dogs is found to be two.

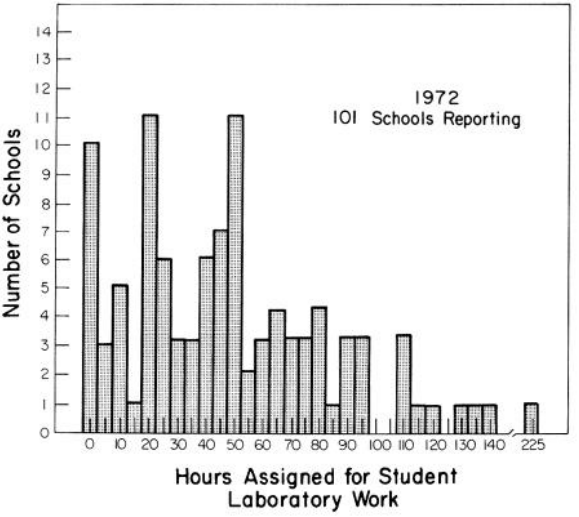

Fig.4. Assignments of time for student laboratory studies for medical schools in the academic year 1971-72.

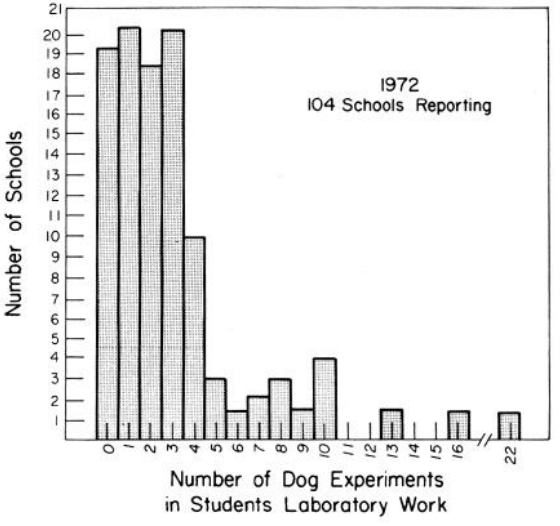

Fig.5. Numbers of institutions reporting the use of the indicated number of dog experiments in student laboratory work in 1971-72.

The use of all other sub-human mammals was found to be small, less than one such student experiment on the average. Exposure to studies on lower vertebrates is also low, approximately one student experiment on the average, among the institutions reporting. These statistics may be contrasted with those of Comroe et al. (3) for 1952 which showed that 72 per cent of the average laboratory time was spent on studies using living intact sub-human animal species.

Data from other sources are available for comparison with these studies. Table 1 presents a summary of data from studies in 1952, 1962, 1966 and 1972. It will be seen that the studies are in harmony with one another, both as to the approximate numbers obtained the same year, and in showing the progressive decline in time devoted to the pre-clinical medical sciences. Data from another study, dealing with time assignments during the 1972-73 academic year, made by the Association of American Medical Colleges (4) have been published. This study indicates that the regular program leading to the M.D. Degree is now 3 years in 16 medical schools, and that 24 additional schools operate with a 3 year optional program. There are now 21 schools in which programs in the basic sciences are now presented predominantly or entirely in an interdisciplinary manner. Nine schools now accept high school graduates into programs integrating pre-medical and medical education.

In the schools with M.D. programs condensed into three calendar years all of the conventional basic science material is condensed into the first year. In addition in virtually all schools contact with patients has been introduced into that year, and newer types of courses, such as human genetics, behavioral science and medical sociology are also being introduced. The result is that student time, in the aggregate, for acquisition of knowledge in the six older conventional pre-clinical sciences has been sharply curtailed. There is general agreement among medical educators that physicians need knowledge in the newly added fields. There is not such agreement with the method being adopted to incorporate such learning experiences, namely by lessening the time avaiable to prospective physicians to acquire at least as solid a base as before in the scientific underpinnings of modern day medicine. It is unlikely that students will be able to acquire such backgrounds in the presently developing scheme of providing less than one year of time, instead of the nearly two years which were conventionally provided in the Flexnerian model of medical education.

The Reasons for Change in Medical School Curricula

The most obvious as well as the most persuasive reason for alteration in the course of training for prospective physicians has been the public unhappiness with the shortage in general of "physicians of first call," and also of physicians of any sort in certain shortage areas. A maldistribution of medical manpower in the United States exists and has been well documented (5). Sparsely settled regions, and populations of high density but low economic status, are poorly supplied with physicians. However, a recent study by Senior and Smith (6) has found, as they say "no unambiguous evidence of a shortage of physicians of the magnitude described" and suggests that "the production of more physi-

Table 1

Median Numbers of Scheduled Total Course and Laboratory Hours

	1971-2 (3)		(4)	1966-7(3)	1961-2	1952-3 (2)
	Present Study	AMA	Aviado	AMA	Present Study	Comroe
Number of Schools	106	Ca.60*	77	Ca.86	74	Ca.70
Physiology	160	168		250	240	>260 <300
Pharmacology		132	>101 <140	162		>180 <220
Biochemistry		150		224		>221 <260
Anatomy		327		556		
Microbiology		142		200		
Pathology		209		330		
Laboratory Hours						
Physiology	45					>101 <120
Pharmacology			<20			>41 <60

*The AMA data for 1971-2 in the field of anatomy represent figures for only 24 schools. Presumably others found it difficult to quantitate their assignments of hours because of interdisciplinary course arrangements, or for other reasons.

cians appears to be an inefficient remedy" for the shortage in certain geographic areas and in specialties.

Legislative appropriations for State medical schools have, in recent years, been tied to stipulations for increased enrollments, and frequently to establishment of special programs for the training of family practice physicians. The current Federal subsidy for individual medical schools is fixed, not only by the numbers of enrolled students, but of the numbers that have recently been added to total admissions, and also to the numbers admitted to new programs designed to shorten total curricula from four to three calendar years for acquisition of the M.D. degree.

The larger share of medical schools in the United States are publicly operated and depend upon State legislative appropriations for their basic support. For the private schools endowment and tuition incomes have become inadequate, and State and Federal subsidies have become relatively larger shares of their total income to cover their operating expenses. Consequently State and Federal legislative stipulations have become crucially important in the real governance of medical schools.

It is not surprising that State Legislatures and the Congress have been searching for ways in which the perceived shortages in medical manpower could be eliminated or at least relieved. Nor is it surprising that medical school administrators, hard-pressed to balance budgets, have responded to public demands, at least some of which they themselves and their faculties perceived as having much merit. A great deal of the public unhappiness with the health care situation today arises from the fact that progressively more physicians choose to practice in narrower specialties. The medical schools, organized as they are into clinical fields and within fields into sub-specialties, constitute the major training ground for specialists and super specialists. The public and its representatives have reacted by demanding more emphasis upon the training of generalists.

Another major force in the movement toward curricular reform in medical schools is the changing attitudes of students. Although medical students are not generally the leaders in the counter-culture movement of the times, they have been influenced by it. In 1971 the number of applicants to U.S. medical schools was 29,172, of which number only 12,335 were admitted (7). The mean scores on the Medical College Admission Tests of accepted applicants have risen in all categories of testing, except in "verbal ability," which showed a drop, which may or may not be significant. In any case it seems evident that students admitted to medical schools have in general attempted to conform to conventional standards of behavior, by serious study during their pre-medical years of work. Statistics as to grade point averages of admitted candidates confirm this conclusion. Of course, this does not imply that all or even most admitted candidates really accepted the conventional view that high grades and academic accomplishment were essential to the training for the profession of medicine. Many of them may simply have accepted the realities of the situation in order to be eligible for admission despite their philosophical objections.

The fact that medical practitioners are among the highest monetarily rewarded professionals at the present time undoubtedly accounts for some of the increase in the number of aspirants to educational opportunities in medicine. However, there are now, as in the past, also many who aspire primarily to careers of human service. Some, one cannot readily assess the fraction, of these are resentful and critical of the science requirements for admission into the practice of medicine. Evidence of this trend appeared at the 1972 Annual Meeting of the Association of American Medical Colleges. The AAMC has in the past been exclusively an organization of Deans or other Executive officers of medical schools. Recently it has added as voting members of its Assembly a small group of representatives of academic societies and a similar small number of representatives of medical student associations. One of the latter presented the following Resolution to the Assembly:(8).

"1. The existence of this exam (Part I of the National Board Examination) and the dependence of medical schools upon its use has caused basic science programs at many medical schools to become inappropriately geared ultimately toward the exam, with an emphasis upon rote memorization, and a relative neglect of conceptual understanding and clinical applications. This emphasis is a major cause of the traditional dehumanization of the medical student, and is thus detrimental to our health care system.

2. The existence of and dependence upon the exam discourages integration of basic science and clinical instruction, since the medical school recognizes it as the first and primary hurdle for the medical student, and therefore, weights its first two years of study heavily toward basic science.

3. There has not been demonstrated to be any significant correlation between performance on this exam and clinical performance.

Therefore, be it resolved that the AAMC should seriously reassess the reliance of medical schools upon Part I of the National Board Exam for evaluation and promotion of students, and consider the possibly adverse influence upon medical curricula that the existence of the Part I exam has had."

This Resolution was not voted upon, but the Resolutions Committee of the AAMC presented a modified version, "Be it resolved that the AAMC assess the reliance of medical schools upon Part I of the National Board Exam for evaluation and promotion of students", which was passed by a large majority vote, dominated by the administrative officers of medical colleges, who, as noted above, constitute the majority of the Assembly.

The major thrust of this Resolution was, quite obviously to question the significance to medical practice of understanding the principles of the basic medical sciences, which constitute the subject matter of Part I of the National Board Examinations. Although the National Board of Medical Examiners may make errors in framing its questions, its whole object has been to provide a mechanism for judging the under-

standing on the part of individual examinees of the scientific foundations for medical practice. To question the successfulness of the examination in achieving its objective is one thing, but to chellenge its objective is quite another matter. It is to challenge the idea that physicians should ideally have solid grounding in the sciences upon which clinical science and art rest.

It should not be supposed that students are alone, in our society, in questioning the validity of the primary assumption on which the Flexner model of medical education was based, that is that physicians should have a sound grounding in the basic medical sciences. The outstanding example of a view comparable to that of some students is that expressed by the Carnegie Commission on Higher Education in 1970 (5). This Commission, a creation of the Carnegie Foundation For the Advancement of Teaching, has presented a report and recommendations which, in essence, repudiate the thrust of the 1910 Flexner Report for the Carnegie Corporation. The 1970 Recommendations call for a general compression of education for the M.D. degree from four to three years and other innovations which would shorten the overall period from high school graduation to the beginning of the independent practice of medicine.

It is of interest to note that no member of the 1970 Carnegie Commission is a physician. The 1970 Report and Recommendations of the Carnegie Commission may have a large impact upon the public and upon academic institutions because of the fact that the same Foundation was responsible for the Flexner report of sixty years ago, which unquestionably was a major factor in ushering in the scientific era in medical education of the last half-century.

The 1970 Carnegie Commission members, as well as many others, have been influenced greatly by the advice of students of educational psychology, many of whom have turned their attention to medical education and its reform in recent years. Many medical schools now have departments devoted to the specific field of educational psychology or have administrative officers whose function is to study and suggest changes in educational methodology. These experts have made studies of the effects of various techniques of education upon test scores of students. They have in general concluded, as is evident from the great decrease in time assigned to laboratory study, for example, that opportunities for extensive laboratory experience in basic medical sciences have no great virtue for students. Considering the high previous academic achievement of most students admitted to medical schools it is not surprising that such students can acquire specific testable knowledge by reading, in other words entirely second-hand information, in less time than would be required to obtain some of it by first-hand experience in a laboratory. However to be able to test for long-term retention and broad comprehension is a different problem. It is certainly possible to evaluate the short-range effects of different educational methods upon measures such as examination scores, but great difficulty arises when one attempts to evaluate the effects of changes upon the major goals of education for a profession, which for medicine are, first of all, to provide the most competent patient care possible for the entire public, and secondly to promote knowledge in the field of medical science. Effects

upon long-term objectives will take a generation to evaluate.

A significant factor in producing the current counter-revolution against the Flexner model of medical education has been the emergence of a large cadre of scientifically trained clinicians, staffing the clinical departments of medical schools. Many of these individuals are quite competent to teach students one or another aspect of the pre-clinical medical sciences. Many also think that they can do the job for medical students better than can persons whose primary interest is in the basic science itself. There is grave doubt, however, that after the novelty has worn off, the most competent of the clinicians will want to continue to spend large fractions of their time in this way.

With the great rise over the last score of years in support for clinical investigation there has been a corresponding increase in the size of full-time clinical faculties, so that in most medical schools voting membership in faculties is dominated by clinicians. Thinking, as many of them do, that clinicians are better able than are basic scientists to assist medical students to learn the basic science relevant to medicine it is not surprising that they have voted to diminish the role of basic scientists in medical education. In some few institutions they have taken over all responsibility for such instruction. In others they have opted for condensed interdisciplinary courses, sometimes incorporating applied clinical science and practice with the basic science material. In still other cases they have chosen to set up greatly abbreviated core courses in the basic sciences, followed by some interdisciplinary matter, arranged in relation to organ systems and their diseases.

The Implications for Society at Large

The last half century has seen an explosive rise in scientific knowledge in the biomedical fields. The rises have encompassed all of the conventional pre-clinical medical sciences as well as some which were not conventional fifty years ago, such as genetics and behavioral science. In morphology the electron microscope has permitted the addition of several orders of magnitude to the possible refinement of analysis of fine structure. Histochemistry has done as much or more for the elucidation of functional anatomy of cells and organs. In biochemistry hundreds of biologically important molecules have been identified and in many instances their functions elucidated in the last half century. Many of these substances have been shown to be involved in disease processes. Simply to mention the vitamins, hormones, enzymes, intermediary metabolites and newer knowledge about essential trace elements and about buffer systems will serve to exemplify and emphasize the importance of sound knowledge about them to the prevention and management of disease. In physiology, microbiology, immunology, pharmacology and pathology similar progress has been made and similar importance has become evident. Genetics and behavioral science, relative newcomers to the basic medical sciences have emerged as having growing importance to medicine. In genetics the dramatic developments in relation to its biochemistry in the last decade leave little room for doubt that it will become a field of major medical importance. As to the behavioral sciences, the very complexity of the problems involved, their

interrelations with neurophysiology, neurochemistry and neuropharmacology, point to the necessity for more rather than less attention being paid to them in the education of competent science-based physicians.

It is ironic that at a time when the competent practice of medicine has become very much more dependent upon science, and more successful because of it, than it was sixty years ago, there should be a nearly uniform trend in medical schools in the United States to deemphasize science in the education of physicians. No one could quarrel with educational psychologists about the virtues of looking for the best methods for acquiring factual knowledge and comprehension, but the superficialization of the basic medical science learning experience that appears to be accepted with complacency by many seems to be incompatible with the rising importance of science in competent medical practice. The easier access to physicians, which may or may not occur in shortage areas with an increased output of physicians, would be a largely illusory benefit if the physicians produced in general are less competent than they could or should be with better scientific backgrounds. It is the public at large that will be hurt if the mine-run of physicians are scientific illiterates. Greater economy for medical students is given as one of the major reasons for abbreviating the medical curriculum by the 1970 Carnegie Commission. The health care bill for the people of the United States is now $80 billion annually. To give full support for one year to each medical student now in training would cost less than 0.05 percent of the current annual health bill. This type of calculation was not, it may be noted, presented in the Commission Report. The fact that the greatest economy easily achievable in the total cost of medical care would be in eliminating unnecessary hospital bed occupancy. Hospitalization costs represent the largest share of all medical care costs. It is probable that a third of all hospital beds are now accupied unnecessarily, for diagnostic purposes and for the convenience to patients and physicians. If economic factors are crucial it is on the care delivery side, not on the educational side that real economies could be achieved without detriment to the excellence of patient care.

There is another hazard to the public in the current trend toward deemphasis on the basic medical sciences in physician education. Elimination or great curtailment of laboratory experience and streamlining and shortening instruction will result in fewer medical graduates having the background which would make them competent to engage in medical research. With lesser scientific background upon graduation the inclination as well as the ability of graduates to embark upon clinical research, most of which today involves the use of basic science methodology and concepts, will probably diminish. If one could believe that amelioration in physician shortage would occur and that deterioration in the quality of medical care would not occur, the public might opt for changes which would slow the rate of medical advance. Since neither of the above two stipulations is more than a hope, and since direct attacks on the basic problems of maldistribution of medical manpower and hospital bed utilization are feasible it would appear that the reformers may be barking up the wrong tree.

The pendulum is still swinging toward the anti-science end of the arc in medical education in most medical schools. This trend seems hazardous to the quality of performance of the mine-run of physicians in the future. There is no evidence available to suggest that the major defects in delivery of health care are related to excessive emphasis upon the scientific underpinnings of medical practice. It would seem to be obvious that at a time in history when the understanding, the diagnosis and the management of disease are more heavily science-based than ever before it would be better to increase the opportunity for medical students to be well-grounded in the scientific foundations of medicine, rather than to decrease such opportunities.

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CNS AND FATTY ACID METABOLISM*

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Glucose serves as the principal oxidizable substrate for the brain under physiological circumstances (7). However, other substrates such as ketones and fatty acids are also utilized by this tissue, both under in vitro (5, 13) and in vivo (1, 8) conditions although the quantitative significance of the latter appears to be secondary (1, 12). In the present discussion some additional information is presented concerning the utilization of free fatty acids (FFA) and ketone bodies by the brain in vivo. Most of these investigations have been taken from studies conducted in our laboratory, and they are used as illustrations rather than as a review of the current status of this subject. Therefore, no particular effort is made to present a thorough coverage of the available literature.

The discussion is divided into five parts:

a) oxidation of subarachnoidally infused isotopically labelled substrates,

b) removal and oxidation of metabolites when administered via ventriculo-cisternal perfusion,

c) estimation of A-V differences across the brain following the administration of tracer doses of the metabolites to be studied,

d) estimation of A-V differences across the brain in newborn puppies, and

e) incorporation of the labelled metabolites into brain lipids.

Oxidation of Subarachnoidally Infused Isotopically Labelled Substrates

In these experiments isotopically labelled substrates (Na-DL-β-hydroxybutyrate-3-^{14}C, or albumin-bound palmitic acid-1-^{14}C) were infused subarachnoidally into anesthetized dogs. Simultaneous cortical fluid, sagittal sinus blood, and arterial blood samples were taken at various times following infusion, as described previously (6). Table I shows that administration of labelled β-hydroxybutyrate (βOHB) was followed by the appearance of radioactivity in both the cortical fluid and blood (9).

Figure 1 represents an experiment in which labelled palmitate was infused (6). It can be seen that the specific activity of cortical subarachnoid fluid was considerably higher following infusion of the labelled

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* Taken from the introductory remarks given at the session on CNS Metabolism at the 1972 Federation Meetings.

TABLE I. $^{14}CO_2$ Specific Activity During the Infusion of Na-DL-β-hydroxybutyrate-3-^{14}C Into Cortical Subarachnoid Space (dpm/μmole)

Minutes of Perfusion

Dog No.	60'			80'			100'		
	A	V	P	A	V	P	A	V	P
1	32	33	567	43	48	963	50	48	---
2	11	13	86	15	17	119	21	22	168
3	9	11	49	11	13	87	13	15	74
4	14	16	481	19	19	506	19	21	731
Mean ± SE									

A= arterial blood, V= blood from sagittal sinus, P = perfusate

metabolite than the specific activity found in sagittal sinus blood which in turn was higher than that of the arterial blood.

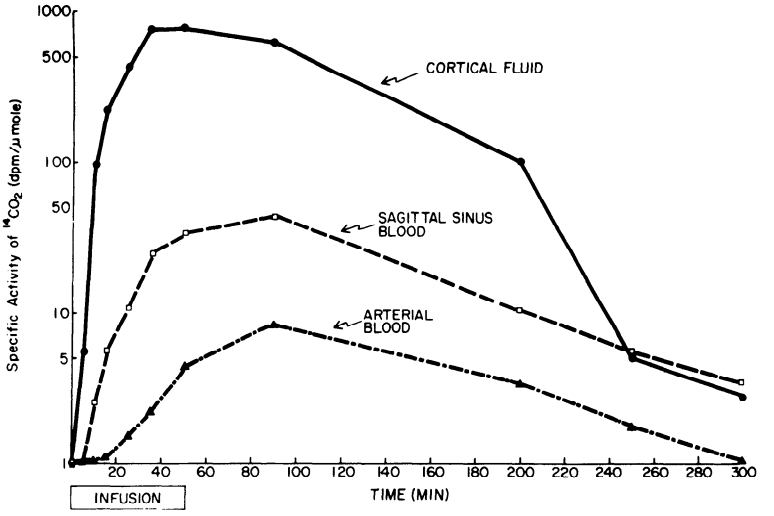

Fig.1. Representative experiment (dog 1) showing changes in $^{14}CO_2$ specific activity during and following a 50-min. infusion of palmitate-I-^{14}C into cortical subarachnoid space.

Although these experiments do not provide quantitative information of the utilization of ketones and FFA by the brain, nevertheless they show the ability of the anatomical area to utilize these metabolites.

Removal and Oxidation of Metabolites Administered by Ventriculo-Cisternal Perfusion

A preparation was developed in anesthetized dogs to perfuse labelled-metabolites containing "mock CSF" through the third and fourth ventricles via an inflow needle in the third ventricle and an outflow needle in the cisterna magna (10). When labelled substrates were perfused in this preparation the specific activity of CO_2 was higher in the perfusate and in the sagittal sinus blood than in the arterial blood. An example of such an experiment using labelled β OHB (14) is given in Table II.

The results of a similar experiment utilizing labelled palmitic acid are shown in Figure 2. Again the specific activity of CO_2 was considerably higher in the perfusale than in the sagittal sinus blood, which in turn was higher than CO_2 specific activity in arterial blood (10).

Table III compares the fractional oxidation of labelled metabolites in the two groups of experiments. It may be seen that approximately 10% of the labelled palmitic acid was oxidized in the course of the ventriculo-cisternal perfusion while only about half of that percentage of

TABLE II. $^{14}CO_2$ Specific Activity of Blood and Perfusate During Ventriculo-Cisternal Perfusion of Labelled βOHB (dpm/μmole)

Dog. No.	Minutes of Perfusion								
	95'			135'			175'		
	A	V	P	A	V	P	A	V	P
1	4.91	24.96	14.41	4.06	37.31	60.00	5.48	27.83	62.05
2	2.80	14.53	18.42	3.21	17.02	31.10	4.31	17.19	32.12
3	NA	NA	22.05	5.98	27.42	34.16	5.60	35.44	32.18
4	5.14	31.19	0	4.86	26.38	15.64	5.44	20.88	21.04
Mean	4.28	23.56	13.72	4.53	27.03	35.23	5.21	25.34	36.85
± SE	±0.74	±4.86	±4.83	±0.59	±4.15	±9.20	±0.30	±4.03	±8.80

A = arterial blood, V = blood from confluens sinuum, P = perfusate,

NA = not available

β OHB underwent oxidation under similar conditions. Table IV documents the fact that almost half of the labelled palmitic acid present in the perfusion fluid did not appear in the perfusate and therefore must have been oxidized, or found its way into the blood stream or was incorporated into brain lipids. About 15% of the perfused β OHB underwent the same fate.

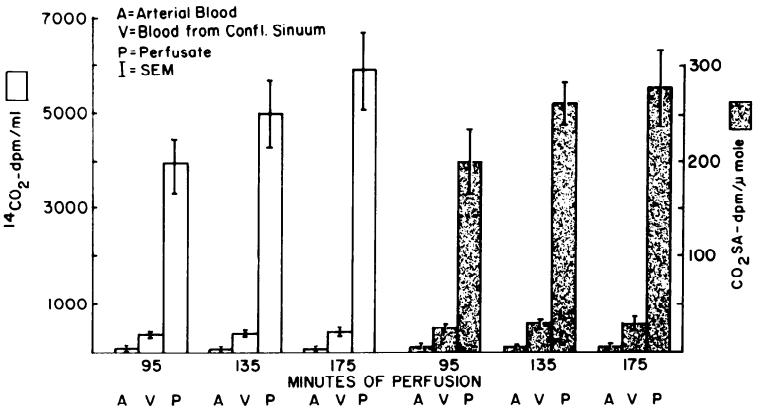

Fig.2. Appearance of $^{14}CO2$ and CO_2 specific activity in arterial and venous bloods and in effluent perfusate (N=8).

TABLE III. Fraction of Perfused Metabolite Oxidized to CO_2 (%)

Labelled metabolite in perfusion fluid	Minutes of perfusion 95'	135'	175'
1-^{14}C-palmitate* (N=8)	8.6% ±2.1	11.0% ±2.8	13.0% ±3.3
Na-DL -3 hydroxybutyrate-3-^{14}C** (N=4)	5.4 ±1.0	6.1 ±1.2	5.1 ±0.8

* Rate of infusion = 50 mμmole/min

** Rate of infusion = 380 mμmole/min

TABLE IV. Fraction of ^{14}C Activity of Perfusion Fluid Recovered in Perfusate (%)

Labelled metabolite in perfusion fluid	Minutes of perfusion 95'	135'	175'
1-^{14}C-palmitate* (N=8)	43.8% ±5.8	56.4% ± 5.7	54.1% ± 4.4
Na-DL-3-hydroxybutyrate-3-^{14}C** (N=4)	70.2 ±5.2	84.9 ±8.2	88.7 ±6.6

*Rate of infusion = 50 mμmole/min

**Rate of infusion = 380 mμmole/min

TABLE V. Metabolite Values (μM/ml) in dogs after 8 Days of Fasting (N=7)

Arterial AcAc	0.109 ± 0.009*
A-V AcAc	0.009 ± 0.007
Arterial βOHB	0.140 ± 0.013
A-V βOHB	-0.020 ± 0.013
Arterial Glucose	7.93 ± 0.31
A-V Glucose	0.72 ± 0.08
E% Glucose $(\frac{A-V}{A} \times 100)$	9.1%
Arterial FFA	1.987 ± 0.276
V-A FFA	0.019 ± 0.066
V-A CO_2	2.20 ± 0.21

*Mean ± SEM

A-V Difference of Substrates Across the Brain

In view of the demonstration by Cahill and his associates (8) that the human brain utilized considerable amounts of ketone bodies during prolonged fasting, the importance of ketone uptake and oxidation in the cerebral metabolism of dogs is of interest. Dogs used in these studies were either fasted overnight or starved for eight days (12). Table V shows that in the starved group no consistent ketone uptake (or FFA uptake) by the brain was observed. Similar findings were also obtained in the overnight fasted group. It should be noticed however, that these animals exhibited relatively low concentration of arterial ketone bodies (certainly much lower than found in humans under comparable conditions). Therefore exogenous DL-β-hydroxybutyrate was infused into these dogs in order to raise the blood ketone concentration (Table VI). During infusion the brain did indeed remove acetoacetate consistently, but the calculated contribution of ketones to the total energy metabolism of the brain was still minor, amounting to about 10 to 12%.

Thus, while the dog brain is able to utilize ketones and other substrates under in vivo conditions these non-carbohydrate metabolites serve only as secondary energy sources for the brain while the primary one still remains to be glucose.

TABLE VI. Metabolite Values (μmole/ml) During βOHB Infusion, 5 mg/kg/min.

	After 1 days' fasting (N=5)	After 8 days' fasting (N=7)
Arterial AcAc	0.470 ± 0.030	0.511 + 0.057*
A-V AcAc	0.055 ± 0.013	0.072 ± 0.023
E% AcAc $(\frac{A-V}{A} \times 100)$	11.7%	14.1%
Arterial βOHB	1.515 ± 0.139	1.329 ± 0.174
A-V βOHB	0.069 ± 0.045	0.164 ± 0.123
Arterial Glucose	4.97 ± 0.16	7.03 ± 0.47
A-V Glucose	0.54 ± 0.10	0.89 ± 0.15
E% Glucose $(\frac{A-V}{A} \times 100)$	10.8%	12.6%
Arterial FFA	0.363 ± 0.040	1.578 ± 0.201
V-A FFA	0.020 ± 0.021	- 0.039 ± 0.137
V-A CO_2	2.09 ± 0.26	2.58 ± 0.27

*Mean ± SEM

A-V Difference of Substrates Across the Brain in Newborn Puppies

Newborn babies exhibit considerable hypoglycemia yet their brain is remarkably resistant to the effects of this condition. Thus it has been assumed that the newborn brain utilized non-carbohydrates quite extensively for energy. These assumptions prompted us to carry out the following investigation on newborn puppies.

The newborn animals (in the first week of their lives) were anesthetized with Nembutal and were infused with radio-labelled substrates for two hours. Towards the end of infusion simultaneous arterial and sagittal sinus blood samples were taken (11). It can be seen in Table VII that the brain of puppies removed both AcAc and βOHB in addition to glucose. The arterial concentration of ketone bodies was much higher in these animals than in their adult counterparts, although the concentrations were rather modest as compared to human levels. No consistent removal of FFA by the brain of these puppies was observed. It can be calculated that approximately 11% of the energy metabolism of the brain may be accounted for by the oxidation of the removed ketone bodies assuming that they were completely oxidized. It appears that the participation of ketone bodies in the energy supply of brain is less in the dog than in the rat (4) where the arterial ketone concentrations are considerably higher.

In the next group of experiments newborn puppies were subjected to the acute stress of starvation for two days in order to assess the relative importance of non-carbohydrate metabolites as energy sources for the brain under these conditions. Table VIII indicates the changes in arterial metabolite concentrations of these animals. It may be seen that the arterial concentration of most of the metabolites decreased, some quite markedly.

Table IX shows the A-V differences of ketone bodies across the brain of these fasted puppies. When compared to Table VII it is clear that the brain of fasting puppies removed only AcAc (and not βOHB) from the blood and that A-V difference of AcAc was not more than in the control puppies.

It was mentioned previously that the brain of control puppies did not show consistent removal of FFA from the blood. Table X presents data showing a consistent A-V difference of FFA across the brain of fasted puppies. Since these animals also received ^{3}H labelled oleic acid, the arterial ^{3}H FFA counts and A-V ^{3}H FFA difference across the brain are also indicated in this table. It may be seen that unlike the fed puppies, brains of fasted animals consistently removed the tritium labelled oleic acid as well.

Although the arterial concentration of glucose is greatly decreased in the fasted puppies as compared to their fed counterparts (Table XI), a marked A-V difference of glucose was observed across the brain in these animals. The A-V difference was less than in fed animals, but the extraction percent of glucose was higher.

TABLE VII. Concentration and Cerebral Extraction of Metabolites in 0-8 Day Old Puppies

Arterial AcAc (μmole/ml)	0.140 ± 0.018*	
A-V AcAc (μmole/ml)	0.034 ± 0.008	N=31
E% AcAc ($\frac{A-V}{A}$ X 100)	24%	
Arterial β OHB (μmole/ml)	0.077 ± 0.018	
A-V β OHB (μmole/ml)	0.023 ± 0.008	N=29
E% β OHB ($\frac{A-V}{A}$ X 100)	30%	
Arterial glucose	7.76 ± 0.72	
A-V glucose	1.17 ± 0.29	N=23
E% β OHB ($\frac{A-V}{A}$ X 100)	15%	

* Mean ± SEM

TABLE VIII. Arterial Metabolite Concentrations in Fasted and Fed Puppies (μmole/ml)

	Fasted	Fed
FFA	0.304 ± 0.046* (9)	0.421 ± 0.049 (11)
TGFA	0.171 ± 0.031 (9)	1.073 ± 0.155 (11)
PLFA	1.238 ± 0.240 (9)	2.537 ± 0.362 (11)
CEFA	0.784 ± 0.114 (9)	0.962 ± 0.101 (11)
β OHB	0.066 ± 0.020 (13)	0.077 ± 0.018 (29)
AcAc	0.086 ± 0.014 (18)	0.140 ± 0.018 (31)
Glucose	2.41 ± 0.40 (22)	7.76 ± 0.72 (23)

* Mean ± SEM; value in parenthesis = N

TABLE IX. Removal of Ketone Bodies by the Brain of Fasted Puppies

Arterial AcAc (μmole/ml)	0.086 ± 0.014*	
A-V AcAc (umole/ml)	0.025 ± 0.003	N=18
E% AcAc ($\frac{A-V}{A}$ X 100)	32	
Arterial β OHB (μmole/ml)	0.066 ± 0.020	
A-V β OHB (umole/ml)	-0.005 ± 0.006	N=13
E% β OHB ($\frac{A-V}{A}$ X 100)	0	

* Mean ± SEM

TABLE X. FFA Removal by Brain in Fasted and Fed Puppies

	Fasted (N=9)	Fed (N=11)
Arterial FFA (μmole/ml)	0.304 ± 0.046*	0.421 ± 0.049
(A-V) FFA (μmole/ml)	0.029 ± 0.007	-0.015 ± 0.017
Arterial ^{3}H-FFA (dpm/ml)	130503 ± 22120	58316 ± 4067
(A-V) ^{3}H-FFA (dpm/ml)	36506 ± 11786	-159 ± 2335

* Mean ± SEM

TABLE XI. Removal of Glucose by the Brain Of Fasted and Fed Puppies

	Fasted	Fed
Arterial Glucose (μmole/ml)	2.41 ± 0.40* (21)	7.76 ± 0.72 (23)
A-V Glucose (μmole/ml)	0.72 ± 0.14 (21)	1.17 + 0.29 (23)
E% Glucose ($\frac{A-V}{A}$ X 100)	41	15

* Mean ± SEM
Values in parenthesis = number of animals in group

The fraction of cerebral oxygen consumption utilized for oxidizing FFA, AcAc and βOHB is indicated in Table XII for both fasted and fed puppies. It can be seen that in the former group FFA oxidation may contribute to approximately one-fourth of the oxygen consumption by the brain while in the fed animals the non-carbohydrate contributors are ketone bodies. However, it is clear from this table that in both groups of animals non-carbohydrate sources represented a secondary fraction of cerebral oxidative metabolism, and that glucose still remained the primary oxidizable substrate. It is not clear from these studies whether this conclusion is peculiar for the dog or is equally true for other species.

TABLE XII. Non-CHO Substrates Accounting for Cerebral O_2 Consumption in Fasted and Fed Puppies

	Fasted		Fed	
	A-SS Diff.	% of O_2	A-SS Diff.	% of O_2
FFA	0.029*	24.3	-0.015 ±0.017	0
AcAc	0.025 ± 0.003	3.4	0.034 ± 0.008	6.0
β OHB	-0.005 ± 0.006	0	0.023 ± 0.008	4.6
		27.7%		10.6%
O_2	2.98 ± 0.26		2.27 ± 0.27	

* Mean ± SEM

Incorporation of Labelled Metabolites into Brain Lipids

It has been observed previously (10) that following ventriculo-cisternal perfusion of labelled FFA the various regions of the brain contained labelled phospholipids even in regions that were quite far removed from the path of perfusion.

Table XIII indicated data from an experiment where tritiated oleic acid was infused directly into the internal carotid artery over a period of two hours. Following such infusion the three regions of the brain studied showed the presence of tritium in the phospholipid fraction. This is similar to the findings of Dhopeshwarkar et al. (2, 3) in mice. Thus FFA are incorporated in the brain phospholipid both from the CSF and plasma.

Similar results have also been obtained in puppies. Table XIV shows that when puppies were infused with ^{14}C labelled palmitic acid and ^{3}H labelled oleic acid (both in the form of albumin-bound FFA) the

TABLE XIII. Phospholipid Fatty Acid Specific Activity in Various Areas of the Brain of a Dog Following 120 Minutes Infusion of ^{3}H-Palmitate into the Internal Carotid Artery

	Frontal Area	Cerebellum	Mid-Brain
PLFA* (^{3}H) Specific Activity (dpm/μmole)	309	332	373

* phospholipid fatty acid

TABLE XIV. Labelled Phospholipids in Various Areas of the Brain of Fed Puppies Following 120 Minutes Infusion of ^{14}C-Palmitate and ^{3}H-Oleate (N=7)

	Frontal Area	Cerebellum	Mid-Brain
PLFA* concentration (μmole/g)	22.1** ±0.9	23.4 ±1.3	27.6 ±1.8
PL ^{14}C counts (dpm/g)	502 ±75	878 ±99	546 ±59
PLFA (^{14}C) Specific Activity (dpm/μmole)	23 ±3	39 ±5	21 ±3
PL3H counts (dpm/g)	4261 ±531	6938 ±598	4914 ±562
PLFA (^{3}H) Specific Activity (dpm/μmole)	191 ±18	303 ±34	177 ±30

* phospholipid fatty acids ** Mean ± SEM

brain of these animals displayed the presence of both labels primarily in the phospholipid fraction. It may be seen from Table XIV that the specific activities of both ^{14}C and ^{3}H were higher in the cerebellum than in either the frontal or mid brain areas.

It has also been demonstrated (11) that following the infusion of ^{14}C labelled βOHB into puppies, phospholipid and free cholesterol were labelled in all the anatomical regions of the brain that were sampled. This is illustrated in Table XV.

TABLE XV. Labelled Phospholipids and Free Cholesterol in Various Areas of the Brain of Fed Puppies Following 120 Minutes Infusion of ^{14}C- βOHB (N=7)

	Frontal Area	Cerebellum	Mid-Brain
PLFA* counts (dpm/g)	624** ±75	1035 ±148	835 ±85
FC*** counts (dpm/g)	995 ±79	1052 ±173	1074 ±415

* phospholipid fatty acids ** Mean ± SEM
*** free cholesterol

Summary

This review describes some investigations conducted in dogs in our laboratory dealing with the metabolism of ketones and fatty acids by the brain. Under in vivo conditions the dog brain is able to utilize both ketone bodies and FFA. Removal of these metabolites may occur either from the CSF or blood. Although the utilization of these non-carbohydrate substrates may be of importance, at least in the dog, they play only a minor role in supplying the brain with oxidizable substrates. This conclusion is based on experiments conducted in both grown dogs and newborn puppies. Although the arterial concentration of the non-carbohydrate substrates influences uptake by the brain, even under conditions of elevated arterial ketones the major metabolite for energy utilization remains to be glucose. Ketone bodies and FFA from either the CSF or plasma are also incorporated into brain lipids, both in adult and newborn animals. The former metabolites are predominantly incorporated into phospholipids and free cholesterol while the latter are found almost exclusively in brain phospholipids. Thus it may be concluded that at least in dogs glucose serves as the primary energy yielding metabolite even under conditions when the arterial (and thus the CSF) concentration of ketones and/or FFA are greatly elevated. It is not clear whether this conclusion is limited to the dog only, or is valid in other species as well.

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NEWS FROM SENIOR PHYSIOLOGISTS

The following letters and notes were received by members of the APS Senior Physiologists Committee in the Fall of 1972.

Born in 1901

Raymond Gregory informed Hi Essex that he is Director of Medical Sciences in the Diagnostic Clinic of Houston.

Chalmers Gemmill to Hi Essex:

I am working in History of Medicine. I have several publications in press.

Joe Hinsey to Hi Essex:

It was might good to hear from you both in your capacity of a Committee member of the American Physiological Society and the personal note. A couple of years ago I was made an honorary fellow of the American Neurological Association, an honor which I prize very highly. I have just recently completed my association with Dr. Aura Severinghaus as a member of his advisory committee in the preparation of his report, "Neurology - A Medical Discipline Takes Stock." In my judgement it is an important contribution which illustrates the advances that can be obtained when federal support is utilized in an intelligent fashion. I have continued my interest in the work of the National Fund for Medical Education in whose founding I was involved. This organization pioneered corporate support of education and was instrumental in establishing the legality for the appropriation of corporate funds to support education in all fields, both in public and privately supported institutions. In today's world there is no sharp dividing line between the two. I continue on the Advisory Board of the Memorial-Sloan Kettering Cancer Center where I had participated actively beginning in the early forties. I have enjoyed very much my work as a Director of the American Hospital Supply Corporation where so much has been and is being done to improve the quality of patient care. The manufacture and development of the Belzer pump and organ maintenance system is just one of the many things they have done. Their American Health Facilities Division is making significant contributions to better organized and more efficient health facilities. I continue to enjoy my contact with many of my former colleagues, students and friends. At the same time I have tried not to interfere with the work of my successors. For those who have been actively engaged in scientific work right up to the time of retirement, there are real values in continuing, many times to advantage in another institution. I do have some advice to those who are younger and active in the work of medical education. I hope they will continue to vigorously oppose the erosion that it is being made into scientific medicine by those who think there are short cuts that can be taken in the preparation of physicians and scientists. In my judgement much that is happening today is taking us back to pre-Flexner days. I realize that I am a member of the Establishment who has worked for half a century for quality in medical education. Although there are continually changes that need and should be made, I am still

proud of what has happened in the advancement of medicine in this country during the last fifty years.

Theodore Koppanyi to Hi Essex:

I am continuing my scientific activities and publish the results in various periodicals, e.g. five papers are in press. I am always interested in a position that would enable me to continue my scientific activities even on a larger scale and I am also interested in an administrative position. However I would not like to move outside the metropolitan area of Washington, D. C. My advice for those who are approaching retirement age is simply plan continuation of scientific and/or administrative activities if possible in the institution from which they retired. This is frequently done, in my case also. Also it is very important to cultivate a hobby preferably of the intellectual type. If one is able, moderate athletic activity is important.

Henry Ricketts to Hi Essex:

Since my retirement in 1967, I have been continuing clinical activities in the form of directing an Executive Health Program at the University of Chicago and have recently added a participation in the faculty health program for the University faculty. For the past five years I have been on the editorial staff of the Journal of the American Medical Association, spending two days a week at their headquarters reviewing manuscripts and writing editorials. My advice for those approaching retirement is to keep busy, preferably with something related to their previous activity, but busy at something in any case.

Jacob Sacks to Hi Essex:

The University of Arkansas has a biphasic retirement system. One may choose to retire completely at age 67, or, the department and administration willing, stay on at reduced responsibility, on a year by year basis, to age 70. I am now ending the first phase, having been on the supposed half-time basis for three years. Actually, it has been half salary, since I've had the same teaching load that I did when I was on full time (salary). I had to give up the chairmanship of the premedical advisory committee which I enjoyed even though it meant a great deal of time-consuming effort. A good deal of that was in trying to convince the premeds who didn't have what it takes to change their sights. I remain as "expert consultant" to the Committee. Commencement comes on May 20, and that ends my duties and responsibilities at the University of Arkansas, although I will be allowed to keep my office in the chemistry building. A few years ago, I was looking forward to the possibility of finding a small college needing a biochemist, but not having enough funds to attract a fresh Ph. D. With TIAA-CREF, social security and income from investments, I could have taken such a job at a nominal salary. However, now that the Nixon administration has greatly reduced the possible job opportunities for fresh Ph. D. 's, my willingness to subsidize such a small college has disappeared. We have over 150 applicants for the position I am vacating. If an administrative position would turn up, I'd be glad to get interested in the possibility

and be willing to relocate. If the position required fluency in Spanish, that would be an extra attraction for me. I have spent a fair amount of time in Latin America, lecturing in Spanish on radioactive isotopes in biology and medicine, and teaching biochemistry in that language. Actually, in El Salvador in 1960, I spent six months setting up the department of biochemistry in the medical school, with Rockefeller Foundation money to equip the laboratory, and with my salary paid primarily by the Organization of American States.

Aldo Luisada to Bruce Dill:

While I am still on the teaching staff of the Chicago Medical School, I have become the Senior Cardiologist of the Oak Forest Hospital. I have a tremendous amount of clinical material and am doing both routine work and clinical research.

Frances Hellebrandt to Bruce Dill:

I am continuing scientific activities after a fashion even though I retired early (at age 55, 15 years ago), have a minor disability and now walk with a cane. I returned part time to Wisconsin, my Alma Mater, after withdrawing from Physical Medicine. There I established a Motor Learning Research Laboratory with special grant funds from the Easter Seal Research Foundation and WARF. I remained there for about five years in a semi-autonomous facility operating under the School of Medicine and the School of Education. We were interested in the patterning of movement under severe exercise stress and in re-studying some of the early observations of Beevor electromyographically. Our papers appeared mostly in the "American Journal of Physical Medicine" which devoted one entire issue in 1962 to our "Methods of Evoking the Tonic Neck Reflexes in Normal Human Subjects," one of the best things we ever did. During this period I began to study the violin because I thought this might be a good way to observe the influence of aging on the acquisition of a complex skill involving the dissimilar use of the right and left upper extremeties. At age 68 I studied briefly with the Hungarian violinist Kato Havas so that I might explore the physiological rationale of her so-called "New Approach to Violin Playing." This led to the publication of a series of papers between October 1969 and March 1971 on the neurophysiological basis of violin playing. These appeared in the British journal for string players called "The Strad." I thought they were lucid and intelligible and important but they made no splash that I could discern. The late Dr. Fenn had done the same sort of thing for wind players through seminars on respiratory physiology at Eastman. These were highly regarded. I am still deeply engrossed in perceptual and motor learning as it applies to violin playing but have yet to find a way to get the message to the musician. All I have gotten from my diligent efforts so far is an invitation to become a Fellow of the Royal Society of Health. My advice for those approaching retirement is to keep the channels open on some milieu where you are known personally if you expect to continue your scientific activities once you step down from formal institutional affiliation. It is a shock to discover the degree to which today's institutional complexities and pressures make it difficult or impossible to share its riches with those who are no longer

in the mainstream of academic life. The Library Committee of one Medical School I visited had voted to keep its doors open only to registered students or card carrying faculty. Keep your flanks protected.

Tom Cureton to Bruce Dill:

I am directing the Physical Fitness Institute, which was created at the time of my retirement here at the University of Illinois, so I walked out on one door and walked into another. We are disseminating materials here, and I am summarizing and publishing work which has been carried on here for some years. Moreover, we are contracting for various clinics around the country, and I have averaged about 30 of these within a 9 month period each year since retirement. Last summer I ran the Applied Physiology Laboratory and conducted what I called the "Scientific Foundations of Physical Fitness" at Brigham Young University. The previous summer I did the same at the University of Oregon. During the coming summer I am a lecturer for the International Olympic Academy at Athens, and will attend the scientific sessions at the Olympic Games in Munich, and also present a paper there.

Ronald Scantlebury to Hy Mayerson:

I retired in 1971 following a 9 year assignment by NIH, to the Department of State. I am now ready to get back into some professional activities, chiefly related to evaluation of research and training programs, International research activities, etc. While I would be available for travel assignments, I would prefer not to leave this area right now except to fulfill an especially rewarding assignment. The following statement about my activities with the State Department appeared in the Cornell College Bulletin: "Dr. Ronald E. Scantlebury '23, who has been on the staff of the Bureau of International Scientific and Technolgical Affairs, Department of State, since 1962, has been responsible for international health matters, maintaining liaison with the departments of Health, Education and Welfare and the National Institutes of Health, coordinating the work relative to the United States-Japan Cooperative Medical Program and coordinating for the Bureau its program relative to support of overseas research by excess foreign currencies held in foreign countries as the result of United States sales of Agricultural surpluses. When Dr. Scantlebury joined the Bureau, the Special Foreign Currency Research Programs added up to approximately $9,000 on an annual basis. The amount proposed for programs covering the current year was estimated at $80 million covering a total of 1500 projects. Dr. Scantlebury had been with the National Institute of Health from 1949 until the time he accepted the position with the Bureau of International Scientific and Technological Affairs."

Victor Johnson to Hy Mayerson:

I really became a renegade physiologist when I went into administration, first at the University of Chicago, then the AMA and finally the Mayo Foundation. Since moving here after my retirement, my scientific efforts have been reviewing revisions of "The Machinery of the Body,"

by collaborators who do all the work. Also, I have been writing monthly articles for the general public in our local English newspaper. I call them "The Science of Life" (a title stolen from H. G. Wells). They deal with biology in general, some physiology for laymen, and some medicine - no medical advice, of course, but mostly the history of great discoveries, such as the diabetes drama, Walter Reed and yellow fever, Minot and Murphy's PA stuff, and things like that. My wife is Argentinian, and we have an eight year old boy, who keeps me busy (and young?) teaching him how to swim and sail on the great beautiful blue Mediterranean. In July we leave London for a three-month cruise of the Far East, Singapore, Hongkong, Manila, China and what else. I am afraid I have no advice for physiologists reaching retirement, except to keep young, keep living, and be interested in something other than the past.

Gordon C. Ring to Hy Mayerson:

In retirement, it is a joy to have time for a little gardening and completing odd jobs that somehow never were finished. I would however, like to be more active in my profession than I am at present and would be glad to go to another area on a temporary basis.

Irv Page to Hy Mayerson:

A large vote of thanks to you and your committee for your interest. The answers are 1) I most certainly am continuing my scientific activities though no longer, to my regret, in the laboratory. I have never found anything better to do! 2) While golf, tennis and fishing are great fun, like liquor, enough is enough. Now that I can afford them, I don't want them as much. 3) I have all the positions I can manage. As Editor of "Modern Medicine" and "The Coronary Club Bulletin", I can indulge my penchant for bitching. Some one of you retirees should set up a business for profit correcting manuscripts for illiterate young investigators. This would help me immeasurably. One of the greatest blessings of retirement is not to serve on committees - I get extremely tired of a posteriori thinking and prefer to do it on my feet. 4) As regards advice to those entering retirement, I can only concoct an old wheeze about work, work and more work with interest and more interest in things intellectual. And don't be overwhelmed or upstaged by the young nor try to emulate them. Their troubles will come soon enough with the inheritance of the national debt. Beware the dogs, Washington, and abundance - including cholesterol. It has now been five years since my heart attack, so if it is comparable to cancer I should be cured. It has been my experience that only very nice people die of myocardial infarction young.

Abe Cantarow to Hy Mayerson:

When, in 1966, the institutional powers-that-be considered it inadvisable to continue to subject me to the stresses of academic life in my declining years, I was invited to seek the safety of anonymity as a small cog in a large bureaucratic machine, where one might remain undisturbed by the turmoil of the outside world, as in the eye of a hurricane. I have been very happily engaged in interesting activities at the NCI ever since. My advice to those approaching retirement is that attributed, I believe,

to Benjamin Franklin: "There is nothing wrong with retirement as long as one doesn't allow it to interfere with one's work."

Arthur Grollman to Hy Mayerson:

As to your questions about myself, I have reached the mandatory retirement age of the Texas University System but have been requested to stay on for another year. Since I will no longer have a laboratory available to me, I would be interested in continuing work in an administrative position either in this area or in any other area of the world.

Victor Hall to Hal Davis:

I am continuing scientific activity in three ways: Supervising a pathological cardiovascular physiology seminar in the division of Pediatric Cardiology; doing editorial work for the UCLA Brain Information; and helping Dr. John Field write a book on the history of American medical education. Keep busy, but don't be afraid to change your field of specialization.

Sarah Tower to Hal Davis:

I am continuing my activities as in the past, namely the practice of psychoanalysis and some aspects of the teaching such as the supervision of cases being seen in psychoanalysis by candidates in the Baltimore Psychoanalytic Institute. I am slowly retiring and also continuing within the framework of my scientific life for the last three decades. May I say that your letters remind me of the important place in my life that my growing up in the American Physiological Society played in developing what has been for me the most important tool in my professional life, namely the capacity to develop and entertain a working hypothesis.

John Welsh to Hal Davis:

My health is excellent and I am thoroughly enjoying country living on the old family farm. A woods operation - selective cutting - kept me entertained this past winter and now the gardening season is beginning.

Howard Bartley to Hal Davis:

I am continuing my scientific activities, though an emeritus. This simply means that I have several doctoral candidates I am still sponsoring, and that I join with colleagues in research and publication. The major portion of my time is spent in writing, however. I have a new book on perception which will be off the press most any day now. One of my writing "projects" is a kind of outlook on man. It has evolved from a many-times rewritten manuscript for a physiological psychology. I don't know whether it will be publishable, but I can't refrain from trying to make some kind of sense out of the many kinds of facts we have today. My advice to those who are a little younger is to retire early or never retire. There seem to be two main channels open these days. They fit two kinds of people. The one channel is typified by civil service

and the military in which one can retire after, let's say 20 years service. People in it are generally those who expect to begin to live after retirement. The other channel contains mostly those who work as long as they can. They enjoy their work and feel that it is worthwhile and rewarding. Some of these people never need to suffer a shift from one preoccupation to another; some have to. For all of them, retirement is a word in a foreign language and is odious.

Alex Sandow to Bruce Dill:

I am continuing my scientific activities full-time just as always.

Emil Bozler to Hal Davis:

It is wonderful that the Society takes an interest in older members. I feel very fortunate that I can continue my research work after my retirement without any change and that I can even do a small amount of teaching. I think it is very important to maintain some useful activity after retirement, preferably one that keeps you in contact with others of similar interests.

Leon Saul to Hal Davis:

I am continuing clinical activities part time and writing articles and books.

Maurice Visscher to Hal Davis:

I am working on calcium fluxes in heart muscle in relation to excitation contraction coupling. I am especially interested in the mechanism of action of cardiotonic agents of various sorts. In addition to my research interests, I am making some studies under the broad category of reciprocal relations between science and society. I am compiling material in connection with the history of the anti-vivisection movement, and I have also started a project looking into the changes occurring at the present time in the methods and content of medical school curricula, especially with reference to the basic sciences. As a first focus in this, I am looking at what is happening to teaching in the field of physiology. I expect to write a summary of this either for the "Journal of Medical Education" or for "The Physiologist." My advice is don't quit work. There are some real advantages in being able to do exactly what one wants to do.

Born in 1902

Will Forbes to Bruce Dill:

I am continuing my scientific activities almost full time. The subject matter is the effects of CO alone, of marijuana alone, and of the two combined on the ability to drive automobiles. We have a specially designed car and the state authorities allow us to use nearly finished but unopened roads for testing. We also run laboratory tests with pursuit meters, visual tests, balance tests etc. We find that each "joint"

of marijuana that you smoke raises the CO Hb by 3%. Will's wife, Anne P. Forbes will continue as an investigator in endocrinology at the Massachusetts General Hospital for another 5 years, and can not take a leave of absence for over 6 months or possibly a year at the most. They wish to be together, so unless an exciting job in human reproduction should turn up abroad for her to work on around 1975 or 1976, Will will be looking for part time jobs in this vicinity from 1974 on.

Otis Benson to Bruce Dill:

I have become "emeritus" at Southwest Research Institute, having tapered off out there last June. I exceeded their mandatory retirement date by a little, but had a small cerebral thrombosis that called attention to the fact that I had reached the Geritol age. I not too secretly suspect that use and abuse of tobacco had a role. If complete "freedom" has any merit I then must say that I am enjoying it. Dawn and I acquired a Holiday Rambler travel trailer and are rarely at home. We spent the month of January in Arizona and have just returned from a shorter sojourn in the Rio Grande Valley. We have a small place on the Texas gulf coast and go there this Monday for a week. Last summer we spent six or seven weeks up in western Montana where I have many old friends, one with a nice ranch on the Big Hole River which is labeled a blue ribbon trout stream. We are in the talking stage now about another trip to the Northwest this summer, possibly to Alaska. Air conditioned or not, it gets damn hot here in the summer. My son is a Lt. Col. in the Air Force and about due to complete a tour of duty in South Vietnam. He has been fortunate enough to get to Bangkok and Hongkong and to avoid injury in Vietnam.

Ash Graybiel to Bruce Dill:

I am continuing my scientific activities. With regard to the soma, I think everyone should become at least an amateur geriatrician, and with regard to the psyche, I think everyone should continue to work on a challenging problem.

Wilbur Selle to Bruce Dill:

I retired from UCLA Medical School, July 1, 1969. Since then I've been on the staff at Long Beach General Hospital, Long Beach. I am now again faced with retirement from the present position and will leave here on May 1 for still other work - group medical practice near my home.

Sid Robinson to Bruce Dill:

I will retire from my regular faculty position at Indiana University in June 1973. However, I shall continue research in the lab here. It is especially important that I get a number of papers written presenting data in our aging study, as well as a few other studies requiring some additional experimental work.

Charlie Puestow to Hi Essex:

I am not continuing scientific activities at this time except to keep two books up to date and to give some advice on research projects to my house staff. I have been retired from the University of Illinois for two years and on February 1 of this year I was retired from Hines. I am continuing my job as Medical Director and Director of Medical Education at Henrotin Hospital which is very interesting and takes little time or energy. Some of our residents from Hines rotate through Henrotin where I keep in touch with their activities. This is important to their training program at Hines, especially because of the large amount of trauma and female surgery we have at Henrotin. The Veterans Administration has made me a Distinguished Physician. This puts me in a consulting capacity to the entire VA and gives me an office in Chicago at a VA hospital where my time is my own and I spend it as I see fit. My retirement from Hines came at a good time because I went through a gastroesophagectomy on January 31 at the Mayo Clinic, operated by Jim Clagget who did an excellent job. However, this kind of surgery is debilitating and it is good to have some free time and to have gotten rid of many responsibilities. As my appointment with the VA as a Distinguished Physician is a three year appointment and as I can keep my job as Medical Director at Henrotin until I am 75 if I wish, I am not now looking for any other kind of assignment. As to advice for those who are approaching retirement, I think one important thing is to anticipate it some time in advance and prepare for it. I recall some of my elders at the Mayo Clinic who worked until the last day of the 65th year without plans for the future and were very much lost when they were retired one hundred percent. There are many administrative jobs in medicine particularly in the field of medical directors of hospitals, which are gratifying and not too time consuming. The best way to keep young is to associate with younger people and that is why a hospital job which keeps a retiree in contact with a young house staff gives one a great deal of satisfaction.

A. R. McIntyre to Hi Essex:

I am quite active as senior consultant in toxicology and pharmacology. This area like most places has its share of drug-abusers; the little spare time I have from this work is spent in writing, sailing and fishing in that order. I also skate in the winter and help Margaret Day (my wife) in the yard when there is grass to cut and dandelions to dig.

Oscar Richards to Hi Essex:

After 30 years with the American Optical Corporation Research I reached retirement age. We then moved to Oregon. The part-time teaching and good facilities brought me to Pacific University where I teach a semester course on environmental vision to the Optometry students and have from one to three graduate students on special problem courses. The course covers seeing problems from outer space to under water, lighting, color vision, etc. not covered by the usual refractive and visual training technics. I hope to get this material into book form before the year is up. Measurements continue on the problem of how

well people 16 years old and over see in terms of acuity and contrast at four light levels from 10fL to moonlight. This should be finished this summer. Last December I received the Prentice Award of the American Academy of Optometry for my work on visual science. Those who do something after retirement all appear happy; those doing nothing usually die early. With so much needing doing in all fields, science and otherwise, those about to retire should find some interesting activities.

Louis Flexner to Hy Mayerson:

I'm still at the old stand and facing up to old responsibilities - teaching in one of the department courses, graduate students and a full load of research. If others are put together like me, my words of advice would be "Keep rowing."

Ray Zwemer to Hy Mayerson:

I have been interested in seeing that American scientists have access to material unavailable to them because of language. After four years with the Federation Proceedings Translation Supplement, the operations were contracted to specialize in Neuroscience Translations. At the end of another four years support was further curtailed and we are working on a two year transition period making the translation journal a commercial enterprise but still retaining the selective aspects of my earlier activities. You may be interested to know that when in the late 50's and early 60's Russian journals were being translated cover to cover there was greater pressure on the editors of those journals to accept articles from important individuals for prestige purposes. I got this information from the late Jacob Stekol after his return from a trip to the USSR where he interviewed 89 persons who had been receiving the Translation Supplement.

James Irving to Hy Mayerson:

Many thanks for your letter of the 14th. It came at an opportune time, since I finally retire from my job here towards the end of next year. I was taken on as Head of the Histochemistry Department here after retiring from Harvard, but am leaving next year and would very much like another job, either in teaching, research or administrative activity. I became 70 the other day but am in good health and active and have a nice research grant from NIH. I am free to move to another area, preferably one a bit warmer! I have during the course of my life taught almost all aspects of physiology, and have been head of three departments, but now I have narrowed down, research wise, to bone and tooth histology, physiology, and biochemistry. The second edition of my monograph on Calcium Metabolism, is just going to the publisher, Academic Press.

John H. Ferguson to Hal Davis:

I've worked into this retirement business gradually, relinquishing the departmental chairmanship in 1967, and my full professorship and project research (Blood Coagulation) in 1970. I continued some teaching

in 1970-71, but have not had any formal assignments this past year under the new departmental chairman. Thus at age 70, I'm resigning my part-time courtesy Emeritus appointment, without any definite plans for continuation of scientific activities. I am giving more time to my shell hobby and semi-scientific illustrated talks to our North Carolina Shell Club and other groups. I'm keen on shore fishing as well as shelling and general beach combing, plus birding and other nature occupations.

John Field to Hal Davis:

In 1971 Victor Hall joined me in the task of preparing an account of medical education in the United States; the facilities and library resources here are well suited to the task in hand. In addition, Sally and I enjoy Southern California. For specific advice may I suggest a joint enterprise with a colleague of the 1890-1904 group. As noted above Victor Hall and I are now collaborating in writing a book, a work stemming from a brief review published in 1970. We have a grant in support of this project. Thus Victor and I are continuing an association that began at Stanford in the fall of 1925 and has continued ever since - except for my three year stint in Washington with the Office of Naval Research and the National Science Foundation. As is so often evident, a career in physiology generates many "post graduate" options.

Rafael Lorente de No to Hal Davis:

My average working time is about ten hours every day of the week and every week of the year. As Professor Emeritus I have a secretary, an office and a laboratory. TIAA and social security take care of my bread and butter. Thus, for the time being, I am fine. However, if taxes keep rising and inflation keeps increasing, not only will I be willing , but I will be forced to move to some quiet town where I can live within my income. I have very important advice, not only for those approaching retirement, but also to those who will approach retirement in the future. Do not fight the establishment. You will be sorry if you do.

Born in 1903

Orville Walters to Bruce Dill:

On September 1 last year I took up responsibilities as assistant medical director for psychiatry at The Methodist Hospital of Central Illinois, where I shall be teaching psychiatry to family practice residents in a new program just established. I am also seeing psychiatric patients in the family practice clinic. Although I became an emeritus at Urbana, I am an active faculty member of the University of Illinois in Peoria, as a clinical professor of psychiatry in the newly established branch of the University of Illinois, the Peoria School of Medicine. The school is under way this year with 17 juniors and seniors. Sophomores will arrive next year from the two new schools of basic medical sciences at Chicago and Urbana, which teach only the first year.

John Nickerson to Bruce Dill:

I have relinquished the chairmanship of the Department of Physiology and Biophysics and am continuing as Dean of the School of Graduate and Post-Doctoral Studies. As I am still a professor in the physiology department, I teach some physiology and am planning to teach some aspects of physics in our undergraduate School of Related Health Sciences. I believe that in anticipation of continued good health and full mental alertness, one must generate some activity for the future years in case that one is compelled by university regulations to retire at some mandatory age. At present, we do not have mandatory retirement at our institution, but one loses tenure at age 65 and is placed on year-to-year appointment.

N. B. Taylor to Hi Essex:

I retire officially August 31, 1972 and would be interested in a position which would permit continued scientific activities. Certain kinds of administrative duties might be of interest and would be considered if offered. I am free to move to another area.

Lathan Crandall to Hi Essex:

In 1962 I went to Southeast Louisiana State Hospital as a resident in psychiatry and at the same time received an appointment as Clinical Professor of Psychiatry and Neurology at Tulane (a unique combination, as far as I know). In 1964, after 1-1/2 years of residency, I was appointed Staff Psychiatrist at Southeast. In the fall of 1971 I was informed that the State of Louisiana would no longer re-employ persons over 65, perhaps because the state was in financial difficulties. I was 68 in October of 1971. Not liking the idea of retirement and believing that I might have something further to contribute I looked about and found that Florida had no age limit. The very new Superintendent of the Florida State Hospital (Dr. Milton Hirshberg, trained in Massachusetts) felt that I might be useful on his staff of some 32 physicians and I came here February 7, 1972 as Staff Psychiatrist. In late April I was somewhat surprised when I was asked to become one of three newly appointed Chiefs of Services, my post being Chief of Women's Services. This may explain why, as I said above, I have been quite busy in recent months. Probably I could not have endured psychiatry in the pre-drug era, but now that we have chemical compounds capable of restoring at least some psychotic patients to approximate normality I find it the most rewarding activity of which I can conceive. The administration here appears to regard my knowledge of drug therapy as above average and I have been lecturing on this subject to the entire staff. I feel needed and useful - what more can one ask?

Sam Reynolds to Hy Mayerson:

I have published two papers since retirement and have three in press, including one for the Handbook of Physiology, Endocrinology. Three are accepted for publication and another submitted this week. I also lecture, - within the past nine months, in Arizona, New Orleans, Chicago, Toledo, Philadelphia and New York. In the course of writing the chapter on the Blood and Lymph Vascular Systems of the Ovary - I found a lot of nice

stuff on the lymphactics, out of France, Germany, and Russia including a book by Etinger of Leningrad. I get in golf which, when I was young I could not afford (remember when the banks closed?) and when I could afford it, I did not have the time. Now, any good or not so good day, I'm out there; the 8th tee is just off our back patio.

Frank Schmitt to Hal Davis:

I am continuing my scientific activities; I devote all my time to the work of the Neurosciences Research Program.

Al Behnke to Bruce Dill:

I am continuing scientific activities and writing chiefly in the field of body composition and body build. During the past three years I have had the opportunity to continue tests and observations with reference to employment of oxygen for decompression and treatment of tunnel workers engaged in the BART project, San Francisco Bay area. I spend about 25% of my time in trying to help young investigators who are working on problems within my sphere of cognizance. I believe that the services of retired physiologists could be better utilized especially to aid young investigators, if they were channeled into a Scientific Information-Action Center. For example, with reference to government contracts in support of physiologic research, the Center would disseminate information as card annotations as to the 1) projects supported, 2) progress made, and 3) bottlenecks restricting consummation of research. The Information Center would provide a "Hans Selye" type of reference service. The Science Action Group would aid young investigators in the solution of problems relating to methodology and interpretation of data. Essentially one would start with an Editorial Board of Retired Physiologists who would serve to Coordinate and Catalyze Research Endeavor of the Young Investigator.

James Pinkston to Hal Davis:

I shall be faced with mandatory retirement (age 70) on August 31, 1973. In the meantime, I hope to be able to continue my teaching and research activities here at the Downstate Medical Center. Upon my retirement, we expect to make our home in Pennsylvania in the Stroudsburg region, and I plan to direct my attention to gardening, hiking and bird watching, while my wife continues her scientific interests in biochemistry at some one of the universities or colleges in that general area.

Paul Hoefer to Hal Davis:

After retirement, I took a job with the Veterans Administration as Chief of Neurology. I am doing some scientific work, but have become mainly a clinician. I might become interested in a position as outlined, and I will be free to move to another area some time this fall. You may publish my answers in The Physiologist. Those of us who have clinical knowledge might do well to apply to the Veterans Administration. The work is surprisingly interesting and the pay is surprisingly good.

Born in 1904

Alan Burton to Hi Essex:

I am on pension, but rehired as a Professor, part-time, in the Department of Biophysics, of which I was the originator, and Chairman for 20 years. I still enjoy teaching a "Survey of Biophysics" course to 3rd-year science students. A few go on to a 4th year in biophysics and an Honours degree in biophysics. In addition I still have one or two graduate students finishing up their M. Sc. or Ph. D. programs. This last year I've managed to finish a new edition of the 1965 book "Physiology and Biophysics of the Circulation," that has had considerable success with medical students and interns (it's now translated into five langiages as well as English). I don't think the new edition is really an improvement, but it gives the appearance of being up to date. I hope that the revision has not lowered its appeal to students, who liked its informality and light, even humorous asides as an aid to concentration in studying its dull parts. In research, at last I'm free to do anything I please. It no longer matters whether others think my effort is worthwhile. (The great Auguste Krogh said this to me about his own work when I visited him in 1945). I have a new and passionate interest in how the proliferation of cells in normal tissue is regulated, and lacks regulation in cancerous tissue (wound healing, regeneration etc. are also involved). Without really knowing anything much about cancer research or tissue culture, I produced a theory of how intercellular communication (discovered and developed by the physiologist, W. R. Loewenstein) could mediate the regulation of growth. Evidently the essay I published on this theory was at least "stimulating", for I've had over 1000 requests for reprints from all over the world. Of course, the experts on cancer are not impressed, and it doesn't tell us how to cure cancer. My graduate student and I require a little more time for this. As for advice to those approaching retirement, I suggest that they do exactly as they please, not what anyone else suggests, i.e. my only advice is not listen to any advice to those approaching retirement. (This is one of the classical paradoxes. If they take my advice, they will not take it!).

Hugh Montgomery to Hi Essex:

I see patients nearly full time, mainly as a consultant in internal medicine.

Ancel Keys to Bruce Dill:

I am now retired as a professor but have research grants and responsibilities, mostly for my epidemiological studies in Europe, covering the next three years. I hope to get a further extension of a couple of years to complete the data gathering, analysis, and publication of the findings in 10 to 15 years of following some 12,000 men in seven countries who were 40-59 when we first examined them. Already many interesting, and we think important, findings emerge, some of which were indicated in American Heart Association Monograph No. 29 (1970, also published as a supplement to "Circulation"). The lowest incidence

of coronary heart disease and of deaths from all causes are found in rural Greece, in rural Dalmatia, in villages in Japan. Blood serum cholesterol, arterial blood pressure, and smoking habits are the outstanding risk factors. Critical analyses, including the use of sophisticated multivariate methods, indicate that no independent contribution to risk is made by relative body weight, body fatness (skinfold thickness), or physical activity. Incidentally, my ongoing program involves writing another book with my wife, Margaret. This is contracted with Doubleday and the title is, "The Mediterranean Way to Eat Well and Stay Well." We hope to finish the manuscript by a year from now after some more field work in kitchens and at the table in Greece and southern France. And we still do not know everything about food in Italy and Spain. My words of advice for those approaching retirement should be heeded twenty years before doomsday. I would advise frugality in the years of best salary, putting everything possible into TIAA, CREF and non-speculative stocks. The pension and retirement programs of our universities are disgraceful, not remotely comparable to the programs in American industry or in the universities of much of Europe.

Leigh Chadwick to Bruce Dill:

I continue to do some formal translating of scientific works from German to English. Have just finished work on the captions for a large book on insects that I started with about 10 years ago. I am not responsible for the long delay. Now McGraw-Hill has acquired the book and is to bring it out this June, under the title "Insects of the World." The author and illustrator is the well-known biological artist, Walter Linsenmaier, from Switzerland. I am extremely happy to know that this magnificant work is soon to become available to all. Not only are the illustrations beautiful beyond belief but the author has brought to his text a fresh point of view, that of the artist, where most of our compendia of equal scientific value have naturally been written from the standpoint of the professional entomologist. My advice to all who would like to be their own boss is to retire just as soon as possible. There is no dearth of worthwhile and enjoyable things to do, both for others and for one's-self.

Hayden Nicholson to Bruce Dill:

I have been here at the American Medical Association a little over four years. I am not sure where we will live after my retirement in August. We might stay here in the Chicago area. Other possibilities would be to return to Miami, where we lived before coming to Chicago, or to go to California in the Sam Francisco area where our daughter and two grandchildren live. I would not be interested in continuing to work after retirement except perhaps on a relatively minor part-time basis.

John Lawrence to Bruce Dill:

The demand of my time from staff and students seems to be greater than ever.

Willard Allen to Bruce Dill:

I retired in 1971 from my post as chairman of the Department of Obstetrics and Gynecology at Washington University in St. Louis. I had the good fortune to head the department for 31 years. After that length of time I found it relatively easy to accept retirement according to the University rules. At the present time I am a professor of Obstetrics and Gynecology at the University of Maryland in Baltimore. While the move from St. Louis to Baltimore was moderately traumatic, I found that the shock of moving has been reduced by the pleasure of teaching medical students again. I do miss the excitement of running a clinical department but the slowed pace here has given me time to write some papers and pursue some clinical research. I find medical students just as inquisitive as ever. Also, despite their long hair, they seem both pleased and grateful when I see patients with them. Perhaps students wouldn't gripe so much if they had more three way clinical teaching, one teacher, one student and one patient! I have only two suggestions for those about to retire. First, they should accept retirement gracefully. Second, they should get another post if possible. I would add a third point for those who retire from chairmanship; they should be out of sight for awhile to give the new chairman a better chance to build a new department.

Jim Shannon to Bruce Dill:

I retired from the PHS Commissioned Officer Corps at the normal "64th birthday." As you know, I was Director of NIH and had been since the summer of 1955. In terms of positions: September 1968 to March 1970, I was Special Advisor to the President of the National Academy of Sciences. March 1970 to present, Special Assistant to the President of the Rockefeller University and Professor of the Biomedical Sciences. Since the pseudo retirement in 1968, I have spent much time on the problems of the National Academy of Sciences, particularly during the past two years as a member of the NAS Council and have served on the Executive Committee of the Council for the same period of time. To complicate life a little more, I have tried to be productive as part of a PSAC panel on biomedical scientific personnel. At Rockefeller, I have been involved in some measure with the problems of institutional planning. Also, with the help of the NSF, I have, during the past year, run a rather interesting lecture-seminar on Science and the Evolution of Public Policy. This will be published by the Rockefeller Press next fall. Other than the above and the usual (though gratifying) honorary degrees and awards, I have tried to keep from being too busy. I find this is a major problem.

E. W. McChesney writes to Hi Essex that he hopes to continue at his present post two more years.

Henry Beecher to Hi Essex:

I am now Emeritus, and I am busy writing a history of "Medicine at Harvard," A history of ideas and their influence on American Medicine. This historical writing is full time and I am enjoying it hugely. The only

advice I could give to anyone approaching retirement is to have something that he really wants to do when that awesome day arrives. I am not continuing my experimental work.

Harry Grundfest to Hi Essex:

I have now reached mandatory retirement age, but will continue to work in the Laboratory of Neurophysiology.

R. K. Richards to Hi Essex:

I have moved out to the West Coast and I am in what I call "active retirement." This means I am holding visiting professorships in medicine, anesthesia, and pharmacology at Stanford University, doing some experimental research, some teaching (pharmacology) and some teaching and clinical consultation in clinical pharmacology at the Stanford University Medical Center and at the Palo Alto Veterans Administration Hospital. My advice is for those who want to remain active in their field to start looking for possibilities about five years prior to retirement.

Paul Sekelj to Hi Essex:

I am still continuing, and expect to continue my teaching and research activities for about one more year. I have not made any plans as yet concerning my post-retirement activities. But I would be interested in doing some literary work related particularly to the history of medicine and physiology, translation and/or abstracting from German, French, Spanish and Hungarian.

Sam Soskin to Hi Essex:

I am still in active practice and while I expect to take it somewhat easier as time goes by, I do not expect to retire until Mother Nature retires me. As a matter of fact, I have recently become the Chief of Staff of the new Century City Hospital.

Bob Woodbury to Hi Essex:

I am still in the harness and happy to still be making my contributions. Our department has grown a great deal since I came here in 1947. We now have 14 staff members, two of whom are shared with other departments, and 11 graduate students. We also have two postdoctorals. Our group has trained 27, I feel, outstanding men to the Ph.D. program. Some are professors, others have positions of lower rank but they are younger graduates. Actually some of our students have trained other men to the Ph.D. degree and they in turn currently have graduate students. I frequently think of the time I visited you in Rochester and also of your visit here to Memphis which provided the stimulus to the administration to provide us with modern animal quarters.

Jim Hardy to Hy Mayerson:

Everything is going fine and we have a busy program under way. True enough, time is passing along and my retirement will be coming up in a year or so. I am delighted to know that things are going well with you and that you enjoy the resolving of "people problems." These are certainly the most difficult to deal with, and it must be that you have a wonderful cardiovascular system to stand the strain. I have no words of advice for my colleagues who are approaching retirement except to postpone it as long as possible.

Vivian Beach to Hy Mayerson:

I've moved to California to be near my brother. I am in a nursing home recuperating from fractured hip and pneumonia. No more scientific activities. Correspondence, TV, reading, eating are my activities. My hand writing has deteriorated, but I am hopeful for better days.

Nathan Brewer to Hy Mayerson:

I still relieve my compulsion to be of some use to society by acting as secretary of the Illinois Society for Medical Research, and by participating in activities related to laboratory animal care and use. I share with Maurice Visscher (and I hope many others) a concern that stems from the myopic view of some tissue culture workers and some other technicians in the biological sciences that would interfere with the proper use of animals to advance knowledge.

R. W. Dougherty to Hy Mayerson:

I am still continuing some research, but find that administrative duties interfere with continuity of problem thinking. I will reach the mandatory retirement age February 5, 1974. I might retire before that time. I would be interested in a position that would enable me to continue my scientific activities. My efforts have been directed to the study of ruminant physiology. I am more receptive to retirement advice than I would be in giving it. From my present vantage point, it seems to me that being busy has many advantages over the "rocking chair."

Evelyn Howard to Hal Davis:

I am continuing my scientific activities; at present my position is quite satisfactory.

T. C. Barnes to Hal Davis:

I am doing research in clinical EEG at Philadelphia State Hospital. I read a paper on EEG bilateral asymmetry at the Federation meeting, April 1972.

Barry King to Bruce Dill:

I am Science Advisor, Division of Community Injury Control, Public Health Service. More precisely - Bureau of Community Environmental Management, Health Services and Mental Health Administration, Public Health Services, Dept. of Health, Education and Welfare. I am interested in research administration, but do not wish to undertake full time employment after retiring from PHS. Geographical areas are not important limitations, but prefer the west coast. I believe we will not divorce ourselves from all scientific activities as long as we are capable of participating and contributing.

Mollie Brazier to Hal Davis:

I am continuing my scientific activities and still have my professional appointment.

Born in 1905

Hal Davis learned that Horace O. Parrack died May 31, 1972. He writes:

His death occurred three days before he was scheduled to retire from active duty at the Aerospace Medical Research Laboratory at Wright-Patterson Air Force Base where he had served, either in uniform or as a civilian since World War II. Throughout this period Dr. Parrack was concerned with the noise problems of the Air Force and made many contributions to the development of appropriate regulations for the protection of personnel and reducing the noise generated over communities near airports. Dr. Parrack was elected to membership of the APS in 1948.

Herb Pollack to Bruce Dill:

I am continuing my scientific activities in spite of the rules and regulations. The George Washington University conferred the title of Emeritus Professor of Clinical Medicine on me but I have arranged to continue to teach. I would not like to lose my contact with students. I have been selected by the American Institute of Nutrition to represent them on the new FASEB Committee, The Life Sciences Research Office Advisory Committee, who elected me their chairman. I do consulting for the Institute for Defense Analyses and just completed a study on desert warfare. I also consult for the Bureau of Radiological Health at HEW, The Executive Office of the President and serve on the Electromagnetic Radiation Management Advisory Council to the Administrator of the Office of Telecommunications Policy. This is most satisfactory. Also I am a consultant to the Rand Corporation. In between times I breed horses and ride to the hounds. A busy life but I am always looking for new areas of interest.

Les Chambers to Bruce Dill:

Your assembly of news items for The Physiologist has provided moments of retrospection as echoes have appeared from people I have

known or worked with or respected during the last half century, but until your chronologically activated note arrived I was scarcely aware that my time had come to be suspected of senior citizenship. The reason is simply that I have not yet been obliged to consider seriously either retirement or the curtailment of a normal (for me) schedule of activity. Four years ago, to circumvent inexorable retirement from Directorship of the Allan Hancock Foundation of the University of Southern California, I elected to participate in the development of the new School of Public Health at Houston, University of Texas, where I am now Professor of Environmental Health and head of a department concerned primarily with human physiological, biochemical, and behavioral responses to environmental change. Development of a faculty, curricular organization, student advisement, and involvement in extramural activities at local, state, and national levels have been useful shields against the imminent concerns of old age. Such free time as emerges is used in pursuit of my long-time stamp collecting hobby, photography, and communication with our four children and five grandchildren. The oldest of the latter group enters Beloit this fall, thus confirming your recorded indication that I was indeed brought into this most interesting existence a long time ago.

Doug Lee to Bruce Dill:

As an Associate Director of NIEHS, my principal responsibility is to keep on top of the activities of the environmental action programs (EPA, FDA, NIOSH, etc.) and the research needed to support them, so that our Institute can take those needs into account in determining its own program. From this basis I have just completed a survey of Federal activities in environmental health research for the Office of Science and Technology, which will go to Dr. David next month. Partly from this basis also I have become progressively involved in editing. In conjunction with the Fogarty International Center we organized the preparation of four texts on various aspects of environmental health. The first, "Metallic Contaminants and Human Health," has just come out. The others are close behind. The Academic Press Environmental Science Series, which I edit, now runs to ten items with several more (including your Festschrift) in preparation. Then there is the proposed APS Handbook on Environmental Physiology. To keep me honest, I have a graduate course on Comparative Vertebrate Physiology at North Carolina State - an interest largely resulting from your prodding.

Josel Szepsenwol to Hi Essex:

I am continuing to teach and to do research, since in our school the administration allows us to stay up to the age of 70, by giving us appointments from year to year.

Sam Leonard to Bruce Dill:

Things go on about the same except that I am relieved of formal teaching and salary. So I consult with graduate students, do research but do not have to plow through waist high snow drifts as on those days past when the show had to go on. At present I will continue "as is" and

do not contemplate moving. I have more opportunity to travel to visit my children and past graduate students which is the greatest of pleasures. Thanks for writing.

Ray Root to Bruce Dill:

I am spending my time doing volunteer work in the Emergency Room of my home hospital; nature studies - identifying birds, wild-flowers, trees, shrubs, and ferns, either on my own or in connection with nature clubs; conservation work; and travelling.

Charlie Hassett to Bruce Dill:

I am trying to direct the activities of 14 civilian and 21 military scientists plus 16 others. The military group is especially young and lively, so that they keep things moving. I have been busier during the last five or six years than ever before.

Burr Steinbach to Hi Essex:

I have "retired" a couple of times, I am now busy in the position noted: Dean of Graduate Studies, MBL.

Theodore Jahn to Hi Essex:

I am not scheduled to retire until July 1973, and I plan to continue working here after that time.

George Stavraky to Hi Essex:

Last year we have taken our two grandsons on a trip to Alaska, and this year we have just returned from a tour of the Galapagos Islands and around South America. It was nice to hear from you and my best regards go out to you all at this time. I have always valued keenly my membership in the American Physiological Society and the friendships and associations which arose through it, and I will follow the progress of our Society with deep interest.

Ray Johnson to Hy Mayerson:

I am retiring at this time from my position as Assistant Dean which I have held for the past seven years. I shall continue on for two or three years (I hope) as Professor of Physiology, to which I will be able to devote a little more time and interest beginning next year, and I shall also continue as Chairman of our Committee for Admission with Advanced Standing, a post which the Dean dreamed up and assigned to me a year ago. Having decided to participate in the COTRANS program, we currently have around 200 applicants from foreign medical schools awaiting decisions which we hope to be able to make primarily upon the basis of their performance on Part I of the National Board Medical Examinations. Teri and I have been taking life easy at home for the past few years, especially after she had a coronary heart attack a little over four years ago. We are currently looking forward to a three-week trip

to the Scandinavian countries early this fall and I am looking forward to a more relaxing and less hectic life here at the Medical School for the next few years.

George Clark to Hy Mayerson:

The only difference between my scientific activities now and before retirement is that in planning a project I am no longer faced with the necessity of proving that it is "mission oriented." I have an adequate office-laboratory and a couple of very small grants which supply needed supplies but no technicians. My wife complains that I spend more time in the lab than ever before.

Joseph Hughes to Hy Mayerson:

I have never retired and I continue to be active - both as a clinical investigator and observer of the problems that interest me that are related to the central nervous system. May we both mutually have the pleasure of having our daily satisfactions outweigh the frustrations.

Don Barron to Hy Mayerson:

As a member of a clinical department I feel far more at home than I did of late years in a basic science, one where the interests were more and more devoted to problems at the cellular level. For one interested in the whole organism as I am the clinical environment is a very happy one for I am in daily contact with the problems without the responsibility for their immediate solutions.

Amedeo Marrazzi in a letter to Hi Essex described his current program at the School of Medicine, University of Missouri: Interdisciplinary basic and clinical laboratories and a research ward have been set up to study the operation of the nervous system in health and disease at the molecular, cellular, organizational and behavioral levels, using drugs to analyze and to correct. A fundamental theory of the manner in which drugs can be expected to and do act on the brain has been evolved and has received support from experiments in animals and in man. The application and appropriate testing of this idea in mental disturbance has resulted in a basic concept of the nature of the disturbance. The findings with mind disturbing and mind correcting drugs have led to a new and productive view of their actions that is consistent with the above. A practical application of the theoretical framework we have constructed has been the devising and testing of a rational, objective (instrumental), quantitative test - a "clinical yardstick" - of mental health and illness and its responsiveness to therapy, that could bring to clinical practice the precision of the experimental laboratory. A new concept of the cellular nature of the learning and memory process has been proposed and awaits test. Continued progress along the lines that have been pursued and the emphasis on investigating the brain cell membrane as the triggering site of cell functions and of their modification by nerve messages and drugs, promises further insights into the brain and mind, better brain drugs and methods of tailoring them, and improved understanding and care of disorders of the brain and mind.

Phil Dow to Hy Mayerson:

I have just passed my 67th birthday and this requires me to be taken off the University System payroll at the imminent end of the fiscal year. Official awarding of the Emeritus title has been recommended but the Regents have not acted on it. When we moved into the new building a year ago this Spring I was ensconced in the paneled chairman's office and during Joe O'Brien's year as acting chairman he insisted on not running me out. Now we are in the throes of search activity and I will have to get space assignment from whoever becomes the new chairman. My grant runs to the end of the calendar year and on it I have a technician who has mostly been working on collaborative projects. Since I got off into editorial work I have never gotten back into the lab very personally. There is a lot of bibliographic work to be done and I am still on Bob Berne's editorial board for "Circulation Research." And while I am around, I suppose I will be asked to help here and there in the teaching. I plan to stay in Augusta, where I have house, friends, outside activities, and probably provision for whatever scientific pursuits I wish to continue.

Herbert Chasis to Hal Davis:

Fortunately, the policy of New York University School of Medicine permits us to continue our activities through our 68th year, and in some instances for some years later. I am continuing my academic activities as Chairman of the Renal Section of the Department of Medicine with the title of Professor of Medicine and my research activities in the Homer W. Smith Laboratory for the study of hypertensive and renal diseases.

Morris Bender to Hal Davis:

I am continuing my scientific activities. Keep active and maintain interest in your work.

Chandler Brooks to Hal Davis:

I am still Dean of the School of Graduate Studies at the Downstate Medical Center and Chairman of the Department of Physiology. Committees have been looking for my successors but without much success and I am not supposed to help. By laws of the State University one must retire from administration at 65, but the law seems to have no liberation clause in it. I can remain as a full Professor until age 70 and possibly beyond. I have a nice laboratory prepared for the day of release from administration, assistants, associates and problems of interest. I shall begin research with my hands again soon, I hope. I shall work on the heart (pacemaker action, integration of action), the autonomic system, neuroendocrine function, and basic processes in the central nervous system.

W. R. Ingram to Hal Davis:

I shall not formally retire until next December or January. I hope I shall be given a room here at Iowa for the warm months, to do some

writing - and gardening. I'd like to spend the cold months in an agreeable climate, preferably where there is a medical school which might loan me a room or a desk and let me use the library.

Born in 1906

Georges Ungar to Hy Mayerson:

I am scheduled to go on until 1976. What happens then will depend on how I feel and how people feel about me. I intend to go on with research and teaching either here or elsewhere as long as I can be useful. In any case, it is pleasant to feel that the Physiological Society watches over us and tries to help us in the crisis of retirement.

Nathan Shock to Hy Mayerson:

The only thing I know is gerontology - so I plan to stay put for the next five years. I'm off tomorrow for Kiev,USSR for the 9th International Congress of Gerontology. Hope to see you at State College in August.

James Bradbury to Hi Essex:

I plan to continue working for two more years until my age 68 retirement on TIAA becomes effective. If someone is on hand to take over direction of the laboratory I will move on out of his way. Possibly I could move to a part-time consultant association. I would prefer to move to a milder climate.

Clinton Knowlton is handicapped by the residual effects of a stroke suffered in 1967.

Harry Schroeder to Hi Essex:

In 1956 I had to give up clinical research because of progressing muscular dystrophy, but my work led me into the fascinating and relatively untouched field of trace elements. So I moved to Dartmouth and Brattleboro and built an unique environmentally controlled animal laboratory for life-term studies on a remote Vermont hill far from pollutants. We have published some 110 papers on this wide-open subject in the past 12 years, and are well-equipped in another laboratory for analytical work on microgram quantities of many metals and metalloids. I am still working on hypertension as part of the project. As I have been confined to a wheel-chair for three years, I don't get to meetings - which in a way saves much time for working, but I miss my friends. We have just had out NIH grant renewed for four more years at a substantial increase, not bad for these times. Don't retire if you like what you are doing. If you don't enjoy your work change your field. Every physiologist knows that organisms deprived of stimuli deteriorate. The human brain is no exception.

Donald Pace to Hi Essex:

Inquiring as to my present status, the retirement age at this insti-

tution is 70 years, so I still have five more years to go before I will have to decide what to do with my time. As a researcher, the Laboratory will always be available to me and I presume that upon retirement, I will be doing the same things I have done most of my life.

Hubert Catchpole wrote Bruce Dill that he will continue his present activities until 1974 when he will be interested in a position that involves research.

Bob Phillips to Bruce Dill:

At the end of the war I transferred to the regular Navy and retired in November 1965. I became Director of the Seato Cholera Research Laboratory in Dacca, E. Pakistan and resigned in December 1970 returning to Taipei. In Dacca we developed a technique for determining bidirectional fluxes of the Na^+ ion across the entire gut in patients with cholera. Here in Taipei we hope to adapt this technique to the study of amino acid absorption across the entire gut in man. The project is funded by the International Foundation. We have a good crew, an excellent well-equipped laboratory and the study is progressing well although a bit slower than anticipated. While I am very happy with my current appointment and research project I would not be unavailable to another appointment if I felt it was more challenging.

Jan Nyboer to Bruce Dill:

I am anxious to continue scientific activities and am free to move.

Austin Henschel to Bruce Dill:

I am still working full time as Chief, Physiology and Ergonomics Laboratory of the National Institute for Occupational Safety and Health in Cincinnati, Ohio. We are applying the skills and methods of physiology to the solution of occupational health problems. Our major emphasis is on pulmonary physiology, work and thermal physiology, vibration and effects of combined chemical, physical and climatic stresses. In addition I direct our international cooperative research projects which are funded under the Special Foreign Currency Program (PL 83-480). I expect within the next few months to shed some of the administrative responsibilities of the Physiology and Ergonomics Laboratory and concentrate more on the foreign program. Hopefully I can then spend a little less time on physiology and more on painting and enjoying the host of interesting and exciting things that are offered for our taking every minute.

Rudolf Thauer to Bruce Dill:

I still have three or more years ahead of me in the Max-Planck-Institute in Bad Nauheim. In our country there are almost no positions for scientists after retirement. Even the editors usually give up their job at the age of 68 or 69.

Richard Tislow to Bruce Dill:

I have very sentimental memories of my life with and among American physiologists: These were "good old times" quite different from present times - although we went through many hardships. Still, I value all those years, perhaps, because it was not so easy in many ways. The last three years prior to retirement from Wyeth Labs, the Company Wyeth let me take a psychiatric residency at their expense. I took it at Temple University Hospital, finished in February 1970. I took a position as a Staff Psychiatrist at the West Philadelphia Community Mental Health Consortium after finishing my residency. Got also an appointment as an instructur in the Departments of Psychiatry and Pharmacology at the University of Pennsylvania. I am very happy in my work as a psychiatrist, until now half time with heroin drug addicts in a methadone maintenance program, and half time in psychiatric emergencies. This work gives me many opportunities for psychiatric observations along lines of dynamic and also behavioral (conditioning e.g.) psychiatry. Presently, I am absorbed by psychiatry which is very fascinating, especially through the satisfaction one gets when people get better, which they do. And also if one can combine it with research how to get people into better mental health. I am very fascinated by your questionnaire and congratulate you on this endeavor! Its very tragic that much manpower is being wasted by throwing people to the side once they get 65, and often years before that. Its great of American physiologists to do something about it. One should think about retirement at a time, probably when one gets into a profession as a young person, but of course, one does not. But probably by age 40, and more so 50, its high time to think about it. I would think: We should have outright scientific workshops, symposia, papers, and research, how to go about retirement. Helpful is the Sunday edition of the New Yotk Times (week in review section; also business section). Kindly keep my name on the mailing list on this subject; I am very compassionate about retirement which creates much unhappiness for many people - where it shoud not. It is also a loss for the country.

Malvina Schweizer Balogh to Hy Mayerson:

As Special Assistant to the Associate Director for Lung Programs, National Heart and Lung Institute, I work harder than ever. I just received a promotion to GS15 in recognition of this.

Smitty Stevens to Hal Davis:

I am just back from England where I picked up the Rayleigh Gold Medal and talked about the processing of loudness in the auditory system. A very pleasant trip withal, including 10 days of skiing in Zermatt. Anxiety is mounting about retirement. Normal checkout time will fall next year unless Harvard decides to grant a year or two of grace. I am waiting to hear the verdict. The administration finds itself so busy appeasing protesters and in-sitters that the minor concerns of anxious professors must fall back to the end of the line. Do I have any advice, you ask, for those approaching retirement? Yes. Try to formulate an exciting campaign that promises to stretch far into the

years ahead. My own project looms as three different books to expound the beauties of a simple power law that seems to relate the strength of the stimulus to that of the sensation. The power law appears to govern all the sense modalities. Accounts are beginning to seep into the textbooks under the rubic Stevens' Law. That in itself is enough to urge me on.

Herbert Jasper to Hal Davis:

I have not retired and I am busier than ever with scientific as well as administrative activities. I am trying to find more time for my country home with sailing and gardening, as well as travel, but have been too busy for any real retirement. I am presently engaged for at least another two or three years in full time occupation and from then on part time in Montreal. It seems to me that a sharp break from the laboratory is a mistake if it can be avoided, partly because of all the friends one has among one's scientific associates. One of the difficult things about judgments of this type is to know when one should withdraw more and more from one's scientific activities, that is when one begins to be able to contribute less than he should.

Robert Morison to Hal Davis:

I gave up my job as Director of the Division of Biological Sciences here in 1970. Since then I have had one of these odd interdisciplinary positions which allows me to think about the interrelationship of science with social affairs of various kinds. It looks as though I would continue this on a part-time basis for the next few years, both here at Cornell and in connection with an outfit in Hastings-on-Hudson, called the Institute of Society, Ethics and the Life Sciences. My observation is that most administrators run out of energy and become resistant to new ideas by that time. A general rule enforcing retirement at a reasonable age is therefore almost a requirement for those who hold the fate of other prople in their hands. Research and teaching are quite another matter, unless one is teaching a required course. I still enjoy what little teaching I do, and I have the illusion that the fact I have lived a long time adds something to the experience of those who listen to me, even in this antihistorical age.

Allan Grafflin to Hal Davis:

I am full-time solo practice of ophthalmology.

Born in 1907

Heinz Specht to Bruce Dill:

I am only consulting, when asked, and not pursuing a research program in my field. I spend my time trying to organize the past both personal and professional, and to catch up on all the things I have put off while I was actively pursuing my work for the PHS. The most satisfying aspect of retirement is the lack of deadlines and the freedom to stop and do what is most entrancing at the moment, including travelling, hiking, canoeing, visiting kinfolk, etc. There is also a large store of

artifacts to work over, including furniture and "objects d'art." I am interested in non-scheduled assignments in assessment of research in the field of applied physiology. We spent a very interesting ten days with Larry Irving at the dedication of the new building for the Institute for Arctic Biology at the University of Alaska in College, Alaska in July-August of last year. There's a lot of physiology going on up there that ought to be of interest to the "Physiologist"! The issues over the matter of the Pipeline are quite exciting.

Dwight Ingle to Hy Mayerson:

Your inquiry finds us at Wabigama, a summer colony club founded by Ajax Carlson, Arno Luckhardt, Andrew Ivy, Lester Dragstedt and friends fifty years ago. We have been members for nine years. Some of the original group remain and stories of Ajax can still be heard any time his name is mentioned. The location is Elk Lake, near Traverse City, Michigan. I gave up the chairmanship of the Department of Physiology three years ago. I stopped research two years ago. I spend most of my time editing "Perspectives" and writing. The department of physiology at Chicago may go out of existence. I am sorry that this is so. I do not believe that all inquiry can be reduced to biophysics and biochemistry. I do not believe that medical students can become good physicians and surgeons without learning about regulation and the integration of functions. However reductive fallacies are in fashion. I retire a year hence. I shall continue to write. I have learned to sail and to race a catamaran. We will continue to spend our summers at Wabigama. Perhaps we shall return to the West for winters. We will not stay in Chicago. I have never liked its dirt and crime but have enjoyed and appreciated the University of Chicago.

Chuck Gell to Bruce Dill:

As you state, it is a far cry from Edgewood days, but I am still active as the Scientific Director of the Naval Submarine Medical Research Laboratory New London, in Groton, Connecticut. The ever present problems in military medical specialties occupy my activities, although they are now largely managerial in character. As for your question regarding any words of advice I may have for those who are approaching retirement, I really have none. Having retired twice already, and in each case having taken the night plane on the day of my retirement to report to my new job, the process of retirement has not had any significance so far. It certainly was a pleasure to hear from you. I believe the last time we actually had contact was in 1948 at Randolph Field when we sat on the first panel to discuss the medical aspects of potential space flight. A lot of water has gone over the dam since then. So far as I am concerned, it is bemusing to think that after spending 30 years in Aerospace Biomedical Research, I now have for the past six years been involved in Submarine and Diving Research. If you can stand an old worn out cliche, apparently I have gone from one extreme to another.

Titus Evans to Hi Essex:

I don't have to retire until June 30, 1976. I would like to continue here until then. However, anytime after June 30, 1973 I would consider going wherever I could be the most helpful.

Robert Gaunt to Hi Essex:

The Research Department of CIBAGEIGY has considerately allowed me to write the prescription for approximately half-time, post-retirement consultant duties. In addition, I have some other outside academic and federal committments. How it will work out remains to be seen but the prospects are highly satisfactory at the moment.

Hebbel Hoff to Hi Essex:

I am continuing my academic interests which for the past five years in particular have been heavily committed to Administration of the College, most recently as Associate Dean for Faculty and Clinical Affairs under Dr. De Bakey as President of the College and Dr. Joseph Merrill as Executive Vice President.

Boris Rubenstein to Hi Essex:

I am practicing medicine and expect to continue. However, I am free to move and would consider another kind of scientific-medical activity within my competence.

Hans Selye to Hi Essex:

I am still continuing my scientific activities and have just been reappointed as full professor of experimental medicine and surgery and director of this Institute for the next four years. I would be interested in a position that would enable me to continue my scientific activities after 1976 but, on the other hand, if a particularly favorable offer were made, I would be ready to move to another (preferably southern) area even before that time. This might be accomplished by maintaining a part-time appointment both in my present and in my future location in order to permit gradual transition without loss of time owing to problems of reorganization. I would not be interested in a purely administrative position, but I would like to find a permanent home for my research library and I could accept the administrative work involved in its transplantation into a new environment. Note: His research library contains over 800,000 titles in the field of endocrinology and stress.

Ladd Prosser to Hi Essex:

I am not yet ready for retirement; in fact I shall not change my status here for three years. I have just returned from a seven-month sabbatical, five of which were spent in the Physiology Department at Monash University, Melbourne, Australia.

Howard Burchell to Hy Mayerson:

I left the Mayo Clinic nearly five years ago to come to the University of Minnesota campus, the reason in part, being thus able to observe and participate in undergraduate education. I am happy that I made the decision to do so though I have not been an unqualified success in the venture. While the retirement age here is 67 (two years longer than the Mayo Clinic), this was not a significant factor in my move. I think that an official retirement age at 65 is still basically a good plan, but because of the shortage of help in the Medical School, made even worse by the change in the curriculum to three years without a summer recess, and the enlargement to a class of 220, I shall stay on another year or perhaps two.

Carl Bunde to Hal Davis:

I am officially retiring at the end of April, 1972 which is mandatory at the age of 65 for the Richardson-Merrell organization where I am employed. Starting May 1, 1972, I am establishing myself as a self-employed consultant in medical research, specifically clinical pharmacology. I imagine my major client will be my former employer. I would be interested in some additional part-time contribution if such an opportunity presented itself. For the past 23 years, I have been in research administration in the pharmaceutical industry with opportunity to do a small amount of direct investigative work of my own. I did some lecturing in pharmacology during the first half of this period, but have not been teaching for the past 12 years. I had never paid much attention to retirement and always was a little impatient with young people who were concerned about retirement. As a result, I was somewhat startled by the paper work required to change from a full-time employee to a retired individual. I would suggest that some of this be planned a little earlier, such as establishing proof of birth date and insurance programs.

Samuel Tipton to Hal Davis:

We are leaving university work and Knoxville. We are building a new home in Long Beach, North Carolina, in the Lower Cape Fear region. We will give up laboratory science and establish a full time Bird Banding station. I have been a weekend bander with the U.S. Fish and Wildlife Service program for 30 years and am looking forward to full time involvement. Our new retirement activity should be a challenge. We will spend part of each fall in residence at the Marromet Bird Observatory in Marromet, Massachusetts. We expect to continue a very active scientific life. Our advice may not be too useful, since we have not yet tested it. I do feel strongly that one should develop active interest in some activity different from one's specialty and retire early enough to pursue it actively and in some depth. I believe the challenge and stimulation are greater if one does not continue in a narrowly specialized field of work after retirement.

Don Lindsley to Hal Davis:

I still am very busily engaged in research activities and have more and better facilities than ever before. We have several pots boiling and think that they contain some goodies. We have completed, or have under way, several studies on thalamocortical relationships, with special reference to the posterolateral nuclei, particularly the pulvinar. It looks as if these problems would keep me well occupied for another three years until I retire, and perhaps even longer in Emeritus status, if life treats me as well in the future as it has in the past.

Robert Kroc to Hal Davis:

Scientific activities are continuing for me, but in a rather different and quite interesting direction. I took "early retirement" from my position in charge of physiological, especially endocrine research at the Warner-Lambert Research Institute in New Jersey. Since July of 1969, the challenge for me has been to evolve a pattern of growth for The Kroc Foundation which was founded by my brother, Ray A. Kroc, who developed and is now Chairman of the fast-food business known as McDonald's Corporation. Currently, there are three areas of activity for the Foundation: 1) Sponsorship of small group medical science conferences at our headquarters on the Founder's ranch in the Santa Ynez Valley, inland from Santa Barbara; 2) A modest grants-in-aid program restricted to research in diabetes, arthritis, and multiple sclerosis; 3) anticipated use of corral and barn facilities on the ranch for a) nutrition studies in cattle as a follow-up of a conference planned on production and grading of animal protein (beef) in relation to its quality for human nutrition; and b) breeding of swine if a pilot study at a western university is promising in developing one or more strains of diabetic swine for use as a (hopefully mini) large animal model. To date, nine conferences, some regional, others national or international in representation have been held. Three monographs have been published to date: Control of Renin Secretion (Plenum), Phagocytic Mechanisms (Intercontinental Medical Book Corporation), and Comparative Pathophysiology of Circulatory Disturbances (Plenum).

Fred Mettler to Hal Davis:

I am interested in consultative and/or short range, specific proposals dealing with problems or publications concerned with the nervous system.

NATIONAL NOISE CONTROL ENGINEERING CONFERENCE AND EQUIPMENT EXPOSITION

Leo L. Beranek, President of the Institute of Noise Control Engineering (INCE), has announced that the 1973 National Noise Control Engineering Conference and Equipment Exposition will be held at the Shoreham Hotel and Motor Inn, 2500 Calvert Street, N.W., Washington, D.C. from 15 to 17 October 1973. Raymond Cohen has been appointed General Chairman for the conference. As the successor to INTER-NOISE 72 held last October, NOISE-CON 73 will be the only national meeting to be sponsored by INCE in the USA during 1973. The format of NOISE-CON 73 will be similar to INTER-NOISE 72 with particular emphasis on noise control applications, including:

Principles of noise control engineering
Clinics to help engineers solve particular problems
Workshops on important current topics
Latest information on instrumentation and equipment
Panel discussions on the Noise Control Act of 1972
State-of-the-art summaries
Engineering papers on latest developments

For further information please write to:

Professor Raymond Cohen
Ray W. Herrick Laboratories
School of Mechanical Engineering
Purdue University
Lafayette, Indiana 47907

LOREN D. CARLSON

1915-1972

Dr. Loren D. Carlson, Professor of Human Physiology at the University of California, Davis, died on Tuesday December 12, 1972 after a long illness. He is survived by his wife, Marion and four children.

He was born on May 5, 1915 in Davenport, Iowa. He received his B.S. degree in 1937 from St. Ambrose College, Davenport, Iowa and his Ph.D. degree from the University of Iowa in 1941. From 1942 until 1946, he served in the U.S. Army Air Corps at the Aeromedical Laboratory, Wright Field, Ohio.

Since 1945 he taught and conducted research, first at the University of Washington School of Medicine in Seattle (1945-60), then at the University of Kentucky School of Medicine at Lexington (1960-66) and finally at the School of Medicine, University of California, Davis.

During his career, Dr. Carlson contributed greatly to the formation and development of all three medical schools with which he was affiliated. He also trained a significant number of environmental physiologists. Dr. Carlson's early work was on enzymes in ontogenesis and the characteristics of protyrosinase in the grasshopper.

Research during the war years in the field of respiratory physiology, led to the establishment of criteria for the delivery of oxygen at altitude. His research in aerospace physiology led to his appointment as a consultant to various offices: The Executive Office of the President, the National Aeronautics and Space Administration, the National Academy of Science and numerous branches of the Department of Defense.

Dr. Carlson's interest in environmental physiology led him to make important contributions to our understanding of the role of the sympathetic nervous system in the regulation of nonshivering thermogenesis and in adaptation to cold. His investigations led to the publication of more than 130 scientific papers.

Dr. Carlson was elected to membership in the American Physiological Society in 1945. He served on the Membership Committee from 1961-65, the Editorial Board of the American Journal of Physiology 1961-65, The Handbook Editorial Committee 1967 - , Council 1966-1970, as President-Elect 1967 and as President 1968.

The XXIVth International Congress of Physiological Sciences, first in the United States since 1929, was convened during his term as President. The American Physiological Society played an important role in what was widely recognized as a highly successful Congress. His selection of the Bowditch Lecture (Physiologist, Vol. 12: No. 2, May 1969) during his term as President represents his long interest in quantitative systems physiology - an interest which he was enabled to develop significantly during his years at Davis.

Significantly, the Handbook of Physiology received renewed impetus during his year as President.

He was President of the Federation of American Societies for Experimental Biology in 1969. He devoted much energy during this time to the creation of the American Biology Council, jointly sponsored by the Federation of American Societies for Experimental Biology and the AIBS for which he held high hopes as a bastion of solidarity for the biological community.

He also served on many national and international panels and committees including the National Committee for the International Union of Physiological Sciences and those of the National Institutes of Health, the Society for Experimental Biology and Medicine, the American Heart Association and the Aerospace Medical Association.

At the University of California, Davis, Dr. Carlson was heavily involved with university affairs. He served on many university and medical school committees and boards, including acting as Chairman of the campus graduate group in physiology. He was also a representative to the Assembly of Academic Senate, the University wide faculty body.

He was the recipient of numerous awards, among them the U.S. Army Legion of Merit, the U.S. Air Force Exceptional Civilian Service Medal, the St. Ambrose College Alumni Award of Merit, the John Jeffries Award of the American Institute of Aeronautics and Astronautics, and the Air Force Office of Aerospace Research Outstanding Achievement Award.

Loren's many friends, who find it hard to accept losing him in what seems such a sudden departure, can be inspired by his determined contributions to scientific pursuits throughout what he knew was a terminal illness.

The LOREN D. CARLSON PHYSIOLOGY SCHOLARSHIP FUND has been established in the Department of Physiology at the UCD School of Medicine by his colleagues and friends.

CARLOS MONGE M.

Dec. 13, 1884 - Feb. 15, 1970

Pioneer in Environmental Physiology

Born at the foot of the Andes, Carlos Monge M. perceived in his youth the scientific challenge of "climatic aggression" offered by the Andes and spent a long lifetime meeting that challenge. His son Carlos Monge C. carries on the pursuit of knowledge in this field of environmental physiology and has given me the basis for this account of his father's achievements.

Carlos Monge M. (M. for Medrano), born in a modest neighborhood of Lima, lost his father to a chronic illness but was fortunate in having an outstanding mother who by teaching piano enabled her four sons to graduate from the University of San Marcos. One son, Juvenal, became a prominent architect, designing several buildings in Lima including the Palace of Justice. A second son, Enrique, became an admiral of the Peruvian Navy. A third son, a scholar who spoke Latin fluently and taught his brothers familiarity with the classics of literature died early. There was love and respect for their mother who firmly believed in the democratic form of government and in equal rights for all Peruvians.

Carlos, rather timid in his youth, was an excellent student in primary school and in an excellent high school from which he graduated in 1902 at age 18. He then entered the School of Sciences, San Marcos University. Two years later he registered in the School of Medicine of San Marcos University, receiving his M.D. in 1911. He often recalled that the main question in his oral examination concerned adaptation to high altitude. He had read extensively in this field including books by pioneers in high altitude research in Peru and Bolivia. He not only did well in his oral examination, he received the highest marks in his class.

Soon after graduation when he was working on a farm in northern Peru he received notice that the Peruvian government had awarded him a fellowship for a year in Europe. He divided that year between Paris where he studied clinical medicine and London where he graduated from the School of Tropical Medicine in 1912. His education and training in Europe coupled with his ability to speak English aided him greatly when he first became acquainted with medicine in the United States in 1914. He visited the major medical centers and became intimate with leading professors including Crohn and Libman at The Mount Sinai Hospital in New York. This proved to be a turning point for medical education in Peru; prior to that visit to the United States professors of medicine in Latin America had looked to Europe for leadership in medical education and research.

While still in medical school, 1909, Carlos joined the Peruvian Army as a physician with the rank of sub-teniente, 2nd lieutenant. In

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Written by D. B. Dill

1927 he was given a part-time appointment as chief of the military hospital in Lima. Later he resigned his commission because of disagreement with General Benavides, President of Peru who wanted to restrict his natural freedom of expression.

Carlos' distinguished career with the University of San Marcos, the oldest in the Americas, began with his appointment as Instructor in Medicine in the School of Medicine in 1914. He rose in rank and was appointed to a professorship in 1931. His genius for administration and his vision of high altitude problems enabled him to found the high altitude laboratory at Morococha, altitude 4,540 m, in 1934. This Instituto de Biologia y Patolgia Andina soon became a mecca for visiting scientists. Although facilities were meager at the beginning a substantial building with excellent equipment was dedicated in 1949; of that, more later. Professor Monge was dean of the School of Medicine, 1941-1945, Rector of San Marcos University 1945-1946. He became Emeritus Professor in 1968. In that year he was appointed Honorary Professor in the new Peruvian University Cayetano Heredia of which his first preeminent student, Alberto Hurtado, was then Rector.

Professor Monge's marriage in 1919 was blessed with three children. The older son, Luis, is an agricultural engineer, the daughter Cristina, studied French in Paris, graduated from the Alliance Francaise of Lima and is now teaching French in Lima. The other son, Carlos graduated from San Marcos in 1948 and based on my advice to his father selected Johns Hopkins School of Medicine for postgraduate training under a Rockefeller Foundation Fellowship. He returned to Lima for high altitude research with Alberto Hurtado and recently when Hurtado retired succeeded him as Rector of the Universidad Peruana Cayetano Heredia.

Professor Monge, a brilliant diplomat, dealt skillfully with successive governments, as well as with leaders in the church. His outstanding skill as a clinician and his friendly spirit stood him well. When his patient, A. R. Leguia, Peruvian dictator was thrown out of office by Commander Sanchez-Cerro, Professor Monge was able despite wide-spread criticism, to have Leguia hospitalized instead of jailed. Paradoxically when Sanchez-Cerro was injured by the followers of the APRA leader Victor Raul Haya de la Torre, Professor Monge was called on to care for President Sanchez-Cerro when he was moribund. Later when Haya de Torre was hiding from the military forces Professor Monge gave him medical care, at the risk of his personal safety. At the same time he was the personal physician of General Benavides, President of Peru and a great enemy of Haya de la Torre. Because of these interlocking connections and his medical reputation he was able to obtain adequate support for high altitude research during successive regimes. This was accomplished without personally subscribing to any particular political philosophy.

Professor Monge's relations with the Catholic Church were cordial although not being a religious man he never became a member of any religious organization. He often remarked that he believed in a superior force which gave man an ethical determination but he had no concept of God. He was firmly convinced that freedom of thought was needed in all walks of life.

During his post-doctoral year in London, 1912, Monge wrote two papers on diseases he had investigated. These were published in the Journal of the London School of Tropical Medicine in 1912 (1, 2). He returned to Lima and a busy period in the Medical School. His achievements seem to have escaped the attention of the Barcroft party in 1921-1922 that travelled by rail from Lima to Cerro de Pasco for noteworthy investigations of the effects of high altitude on man.

Several clinical papers were followed by a noteworthy account of chronic mountain sickness published in Paris in 1929 (3). This disease proved of special interest to Talbott who described two cases he observed in Chile incident to the 1935 International High Altitude Expedition. Talbott recognized the primary description given by Monge and proposed the designation, Monge's disease.

Monge's first papers published in the United States appeared in the Archives of Internal Medicine in 1937 (4), in Science in 1942 (5) and in Physiological Reviews in 1943 (6). Then in 1948 his classic book, "Acclimatization in the Andes" was published by the Johns Hopkins Press (7). The introduction was written by Isaiah Bowman, President of the Johns Hopkins University and a distinguished geographer well known to Monge because of his explorations in Chile described in his monograph, "The Desert Trails of Atacama." In later years Monge gave more attention to the social sciences (8). Among his last publications are two books which were shared with his son as author. These dealt with high altitude diseases (9) and with adaptation of domestic animals to high altitude (10).

To a scientist convincing evidence of success lies in the accomplishments of his students. The first of Monge's many outstanding students, Alberto Hurtado, came to Harvard Medical School, graduating in 1924. He was a Rockefeller Fellow with George Whipple at Rochester, 1941-1942, after which he returned to his appointment in the School of Medicine, University of San Marcos. Professor Monge once told me that he had chosen Hurtado as the best qualified of his students to transform medical education in Peru from the French system to the United States system. Hurtado undertook this with vigor and determination. Changes took place although he was impatient at the slowness of pace.

A second of Monge's students, E. S. Guzman Barron graduated in medicine at the University of San Marcos and after a few years at Johns Hopkins Medical School was appointed an assistant professor in biochemistry with Baird Hastings at the University of Chicago. In 1935 Hastings proposed him as a member of the International High Altitude Expedition to Chile. That was a happy arrangement. He was capable as a scientist, an expert in human relations and able to talk the language whether to the miner or to major-domo. He saw to it that no diplomatic errors were made in our stopover in Lima; there I met Professor Monge for the first time. Two others of Monge's students were research fellows in the Harvard Fatigue Laboratory in the 1930's, Humberto Aste-Salazar and Leoncio Contreras. By this time Hurtado was well embarked on his own career in high altitude physiology, centering his studies at the high altitude laboratory established at Morococha in 1934. The publications

by Hurtado and his dozens of students have established him as a dominant leader in the field.

Scientists also are gratified by the honors that come to them. These came early and late to Professor Monge beginning with his selection for a government fellowship in 1911 for study abroad. He received the national award in Medicine in 1911, 1912, 1936 and 1968, a span of 57 years from the first to the last.

He was an honorary member of many Peruvian Medical Societies and was elected to the Argentine Society of Medicine and to the Chilean Society of Medicine in 1934. He was an honorary professor of the Universities of Cochabamba and La Paz, 1947. His greatest honor came in 1941 when he was appointed Doctor Honoris Causa by the University of Chicago as an important feature of the celebration of the University's 50th Anniversary. Finally the American Physiological Society elected him to Honorary membership in 1952; seven years later Hurtado received the same honor.

Reference was made above to the new building for high altitude research dedicated at Morococha in 1949, the Instituto de Biologia y Patologia Andina. Hurtado was Minister of Health in 1946-1948 and knowing full well that his ministry might have short life, succeeded, during his ministry, in gaining both approval and funding by the government.

Dedication of the new building was planned as part of the International Symposium on the Biology of High Altitudes, scheduled for November 23-30, 1949. This was sponsored by UNESCO and the Peruvian Government. Monge was chairman of the organizing committee and Houssay of Argentina was honorary chairman: I was privileged to attend and since this provided an opportunity to see Monge and Hurtado in action under somewhat trying conditions some details of the affair are included in this biography of Monge. The situation was complicated by displacement of Hurtado as Minister of Health by a senior Army medical officer with no background in high altitude research.

The United States Air Force through its School of Aviation Medicine had supported high altitude research by Hurtado and his associates so the United States sent an official delegation of six headed by Major General Harry G. Armstrong, Surgeon General of the Air Force. Eighteen others made the flight set up by the Air Force. Included were medical officers in the field of aviation medicine and physiologists who were expert investigators in biological fields related to high altitude. I quote from the synopsis of the affair I wrote for Science, Jan. 6, 1950.

"The program centered around man at rest and at work in the environment's characteristic of different altitudes. The subjects included adaptation and acclimatization to altitude in man and animals; the acute and the chronic effects of altitude in rest and work; the relations between fertility and altitude; and the special problems of aviation medicine.

"About half of the scientific program was devoted to 15-minute papers, with plenty of time for discussion. In other sessions, experts

led round table discussions of selected general topics. Some papers were presented in English. A translated summary of Spanish papers was frequently provided. These, with brilliant off-the-cuff translating by Albert Hurtado of the Andean Institute and E. S. G. Barron of Chicago, lowered the language bar to interchange of ideas.

"Dr. Monge philosophied on the Incan organization for protecting their people against what he termed climatic aggression. Physical training was made a routine part of living; wedding ceremonials favored survival of the fittest; the colonization system recognized the phenomenon of acclimatization. Dr. Monge also described chronic mountain sickness, first recognized by him in 1928 and now known as Monge's disease. It illustrates failure to resist climatic aggression and its specific cure is residence at sea level.

"Dr. Hurtado led a stimulating discussion of chronic anoxia as seen in the Indian miner at Morococha, 14,900 feet. His acclimatization depends on ancestry, on uninterrupted hypoxia from the beginning of fetal life, and on hard physical work. In his acclimatized state, he exhibits hyperventilation, appreciable in rest and marked in exercise; increased alveolar volume; normal pH; polycythemia; normal resting cardiac output; and greater vascularity of tissues. At that altitude the Indian miner has as great a work capacity on the treadmill as the Indian at sea level, and he is more efficient. This new finding has raised unsolved questions about the possibility of fundamental changes in the biochemical processes of energy transformation.

"In a study participated in by Dr. Rotta, it was found that the Morococha miner has an absolute as well as a relative increase in blood hemoglobin. He has three-eights more red cells per unit volume of blood and seven-eights more red cells in circulation. His blood volume is two liters greater; the increase is entirely red cells. In terms of hemoglobin he has about 1,450 grams, as compared with about 800 grams in his sea-level cousin.

"The dynamic state of man is well illustrated by his hemoglobin response. A new balance must be struck between rate of formation and rate of destruction; this balance must also adjust to the increase in the capillary volume. This process and the numerous other steps in acclimatization take months, possibly years, for attainment of equilibrium. Sometimes there is failure of some element. Then physiology retreats before pathology.

"Through the hospitality of the institute, the delegates were privileged to visit the remarkable high altitude laboratories at Huancayo (3,200 meters). Morococha (4,540 meters), and Tiolio (5,030 meters). The party witnessed the dedication of the new building of the Morococho laboratory. These laboratories have been made possible by the government of Peru, the Rockefeller Foundation, and Don Manuel Pielago of Huancayo. Staff members expressed the hope that scientists interested in any phase of high altitude biology will make use of the laboratories.

"All of the delegates were impressed by the high quality and wide range of the institute's research program, the excellence of laboratory facilities at Lima and at altitude, and the generous hospitality of the people of Peru. The Institute of Andean Biology will undoubtedly become as famous internationally as the Naples Biological Station, the Jungfraujoch, and the Woods Hole Biological Laboratory."

Knowing the circumstances would have made the attendance at the dedication a traumatic experience for Hurtado, we were not surprised at his absence. We were puzzled by the absence of Monge who sent his daughter Cristina to accept the keys to the building from the Minister of Health. Later Carlos explained to me that he did not attend because it would have aggravated the trauma for Hurtado.

The Symposium ended on a happy note. Our party entertained our hosts at a banquet at La Lagunita in Callao, Lima's seaport. We invited the wives to the party, an unusual and happy experience for them (one of them confided in me that under such circumstances husbands thought the place for wives was in the home). Professor Monge, guest of honor, made some appreciative comments in grand style. The next evening he saw us off: I'll always remember the affectionate embrazo.

A great source of happiness for a scientist is to become an authority in a field of research. More joy comes when his students follow in his path and then blazen new paths. So Professor Monge took great pride in Hurtado's outstanding achievements. After establishing a new University in Lima coupled with a new high altitude laboratory at Cerro de Pasco, Hurtado has now retired as Rector of the University to devote full time to the preparation of a monograph on high altitude. This will summarize the extensive investigations, published and unpublished, on the physiological and patho-physiological aspects of life at high altitudes. His student Carlos Monge C., has succeeded him as Rector of the University. My last letter from Professor Monge was dated Nov. 7, 1969 about three months before his death. I had congratulated him in anticipation of his 85th birthday. He wrote, "Your greeting gives me a great opportunity to have another bottle of wine on my birthday, remembering you." He closed with words expressing pride in the achievements of his son, "My son is doing fine. He was appointed on the High Altitude Committee as Chairman during the last International Congress of Physiology and later took part in a high altitude symposium in Aspen, Colorado."

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REQUEST FROM DR. FRAZIER

Dr. D. T. Frazier wishes to acknowledge Dr. David Holcomb, Dr. Fred Zechman and Gail Hillenmeyer for their contribution in the publication of "Computer-Assisted Self Evaluated Tests for Medical Physiology" published in the November 1972 issue of The Physiologist (Vol. 15, No. 4, 360-367).

LETTER TO THE EDITOR

In recent years, Physiology as a visible and separate profession has been subject to considerable duress in some medical schools. Core curricula, elective programs by organ system, integrated teaching by committee, have all contributed to its decline as a separate profession and may be paving the way toward its disappearance as an administrative unit in some medical schools. Further, what Physiology is, what is taught, and how it is taught has also come under review by administrators and non-physiologists. I would remind you of Dr. Robert Pitts' eloquent plea in The Physiologist for the survival of the teaching laboratory in Physiology. Now in a recent documented report Dr. Maurice Visscher has added his voice of concern. (Dr. Visscher's report appears in this issue).

All of these problems make it necessary for our society to assist in the establishment of the necessary criteria for accreditation of Physiology teaching and course content at medical colleges. Up to now we have left this responsibility to the individual departments of Physiology in the different schools of medicine. The only organized attempt to establish uniformity of performance has been through the National Boards which has established its own panels of experts and testing procedures.

If present trends continue, those responsible for the administration of medical education will need all the guidance possible to assure themselves that students of medicine will receive an education in the basic sciences sufficient to prepare them for the practice of medicine. As an organization of professional physiologists, it is our responsibility not only to assist in the establishment of guidelines for effective teaching of physiology, but through accreditation with input from a prestigious professional organization such as ours, to assure that the highest standards of education in the basic sciences is maintained within the medical curriculum.

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