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Collection/Office of Origin: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files

OA/ID Number: 62038
Folder ID Number: 62038-001

Folder Title:
Life Sciences: General [1 of 4] [1991]

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Position:

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"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9121802
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

FROM: OLKEN, Hyman: OLKEN PUBLICATIONS

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 06/01/91

SUBJECT: RE: AN ADVANCE IN BIOLOGY OF THE BRAIN THAT WOULD
GREATLY ADVANCE PROGRESS IN SCIENTIFIC UNDERSTANDING
OF THE BRAIN.

DIRECTORATE STAFF
ASSIGNED: ASSIGNED:

ACTION STAFF
REQUIRED: ACTION:

SENDER'S DUE DATE:
OSTP DUE DATE: STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

COPIES TO: LIFE SCIENCES

WHITE HOUSE TRACKING #: CONTACT PERSON:
REMARKS: PHONE: EXT:

OSTP RECEIVED: 06/19/91
DEPT RECEIVED:

FILE: *P* LIFE SCIENCES

OLKEN PUBLICATIONS

2830 KENNEDY STREET • LIVERMORE, CA 94550, USA • PHONE (415) 447-5177

912K602
RECEIVED

91 JUN 19 P 3:16

June 1, 1991

OFFICE OF THE
DIRECTOR

Mr. D. Allan Bromley
Presidential Coordinator
Decade of the Brain
Washington, DC 20500

Dear Mr. Bromley:

Science magazine in the current issue (May 10, 1991, page 775) reports that you will be directing a large-scale revamping of the biological sciences of the brain. I would like to suggest something that would make your task easier.

Some years ago (in 1963) I conceived an advance in biology of the brain that would greatly advance progress in scientific understanding of the brain. The concept is that nerve cells in the cortex form clusters which act as single electrical units. These units perform different electrical activities. Such clusters can operate as amplifiers, as oscillators, or as dc/potential generators (flip-flops). My concept is, furthermore, that these clusters can shift from one of these electrical functions to another without change of the electrical circuits involved. The change from one electrical function to another is accomplished, not by circuit changes, but by changes of blood supply to the neuron cluster involved. This is a concept of tremendous power to advance our understanding of the human brain.

At the time I evolved this concept, I also conceived another one, as follows. The human cortex comprises two major anatomical formations. One formation comprises deep layers of large nerve cells (pyramid cells). The other half of the cortex comprises deep layers of tiny (granular cell) neurons. In the period of nearly one hundred years since research on the human cortex began (Cajal), the researchers all studied the layers of large neurons. The other half of the cortex, comprised of granular cells, was totally ignored by the entire research

profession. In fact, the number of papers on the tiny granular cells could be counted on the fingers of one hand.

This was a tremendous error by the neurological profession, so to correct it I wrote a paper which provides a basic understanding of the granular cell neuron masses - what they do, how they work, and by what methods they can be tested and studied. I combined these two advances - the concept of conversion from one electrical unit to another without change of circuits, and the concept of granular cell neuron masses - into a single paper entitled "Granular Cell Neuron Masses".

Unfortunately, to publish this paper I did not follow the conventional practice of presenting it at a neurological conference. Instead, being an electronics engineer, I presented it at an electronic engineering conference. They accepted it, gave me fifty minutes on the podium, and published it in the proceedings of that conference (MAECON - Midwest Aerospace and Electronics Conference, held at Dayton, Ohio, May 1963). Neurologists do not read literature in electronics engineering, so the valuable concepts provided in this paper have lain dormant for 28 years!

Recently (in 1989) I moved this material into the neurological literature field by publishing a little book on "The Physiological Mechanism of Memory in the Human Cortex" in which I included this paper on granular cell neuron masses as an appendix. However, this has gained very limited publications - only the dozen copies of that book that have been sold.

I believe that if you will make the concepts contained in this paper on granular cell masses more widely known, this will create an immense advance in the science of the brain.

I would be pleased to send you a copy of my paper on the Granular Cell Neuron Masses.

Sincerely,



Hyman Olken

HO/klr

"LIFE SCIENCES (CORRESPONDENCE TRACKING)"

TYPE: ACTION DOCUMENT NUMBER: 9121672
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

FROM: SONDORP, Herman: SOUTH AFRICA

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 05/27/91

SUBJECT: REQUEST, IF INTERESTED, TO DISCUSS HIS WORK WITH
REPRESENTATIVES, EITHER FROM THE U.S. EMBASSY OF
FROM THE USA REGARDING HIS RESEARCH INTO HUMAN
HEALTH: THE EUONTOGENETICS PROJECT.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED: D.A. Henderson

ACTION STAFF
REQUIRED: AS APPROPRIATE ACTION: Comments to DAB

SENDER'S DUE DATE:
OSTP DUE DATE: 06/21/91 STAFF DUE DATE 06/21/91
DATE COMPLETED: DATE COMPLETED/DEPT: 06/25/91

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS: Originally sent to DLS for necessary action; Dr. Bromley on
06/11/91 asked Dr. Henderson for comments.

CLOSED

OSTP RECEIVED: 06/07/91
DEPT RECEIVED: 06/12/91

FILE: P- LIFE SCIENCES

9121672

RECEIVED

91 JUN 7 AM: 04

OFFICE OF THE
DIRECTOR

P.O. Box 91048
Auckland Park
2006
South Africa
27 May 1991

Allan Bromley
Science Adviser to
President George Bush
The White House
Washington
United States of America

Sir

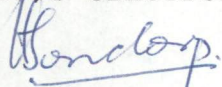
Research into Human Health: The Euontogenetics Project

It has rightly been said that the problem of breast cancer, for example, is of such a serious nature that should there be even the slightest possibility that an answer to the problem might be forthcoming, that possibility should be given the highest of priorities and be thoroughly examined until either an affirmative or a negative answer could be ascertained.

The theory described in the enclosed brief summary holds such a possibility, not only to a solution to the problem of breast cancer, but to that of a number of other diseases as well. Due to the large scale integrative approach in the study, as opposed to the reductionist approach employed in most scientific studies, the work can only be published in the form of a book or a treatise with an accompanying set of charts, hence the reason for me not so far having published it in a scientific journal.

If any of the research instances in the USA would like to pursue the ideas contained in the work, I am prepared to discuss the work with representatives, either from the USA Embassy or from the USA. Unfortunately I am not in a position to travel overseas myself.

Yours sincerely



Herman Sondorp

Euontogenetics: The Science of
Normal Growth and Development

Memorandum

by

H. Sondorp

Introduction

Primitive peoples such as the Bushmen or Khoisan, the Eskimo, the South American Indians, the Australian Aborigine, the Central African Pygmy, and various other African tribes are healthy, i.e. free of the so-called 'diseases of civilization', not primarily because they have a more placid and therefore less stressful way of life, nor because they have a more natural and unrefined diet, nor because they generally get more exercise, but because their methods of infant care are still in line with those of our Stone Age ancestors' to which man and also the human infant had become adapted to in the course of man's evolutionary ascent.

Modern man by contrast is prone to the so-called 'diseases of civilization' - including degenerative diseases such as cancer, heart disease, hypertension, rheumatoid arthritis, chronic bronchitis, diabetes, asthma, allergies and autoimmune diseases, various endocrine disorders, and various neurological and mental disorders such as migraine and headaches, sleep disorders, schizophrenia, depressive psychoses, etc. not primarily because of the customarily blamed factors such as stress, psychosomatic influences, wear and tear, air pollution, food additives, dietary excesses or deficiencies, lack of exercise, fatigue, lack of sleep, smoking, drinking or drug abuse, but because certain factors in the modern-day methods of infant care, and in the modern environment in relation to the methods of infant care, differ too drastically from those conditions under which our Stone Age ancestors had evolved and had become adapted to.

These are two of the main conclusions from the study entitled "Euontogenetics: The Science of Normal Growth and Development".

For more than ninety-nine percent of human history man lived as hunter-gatherer, roaming in small flexible bands. In daytime the men were occupied mainly with hunting activities, whilst the women spent part of the day roaming in small groups gathering plant edibles, loudly chatting and singing as they went along, the remainder of the day being spent in the shade under trees busying themselves with their daily chores. Temporary shelters were used only for sleeping in at nighttime. It was therefore essentially an outdoors and sociable way of life.

Mothers with infants carried them or lead them along whilst gathering, or the babies were left in the care of elderly women in an extended family system. The babies were breast fed on demand, and at nighttime the infants slept in close proximity to their mothers enabling them to nurse at the breast even without the mothers waking up. It is to this sort of ecological niche that the human infant became intimately adapted to in the course of man's evolutionary ascent - of being carried by the mother, spending much of the day in an outdoors environment in an intrinsically social setting, and being breast fed on demand.

With the advent of farming and animal husbandry about ten-thousand years ago, leading to a settled existence and consequently to indoors living and so to the rearing of infants in 'cots', certain very drastic changes were introduced in the methods of infant care and so in factors affecting the processes of growth and development in the young infant. Some of these changes are quite obvious, but some work very subtly indeed. The outcome of all this is that the normal developmental processes pertaining to the neuro-endocrine system, the immune system, the intermediary metabolism, homeostasis, circadian rhythms and the biological clock, and ultimately also the genetic processes are all to various degrees being affected - being either retarded, undercut, polarised, shunted or misdirected in the young infant, so leading to a state of physiologic degeneracy and a constitutional predisposition towards disease in the ensuing child, adolescent and adult.

This is part of a more extensive study, also including a comparative study of prenatal influences on the development of the embryo and fetus, and is centered around a set of charts, one of which is entitled

"A Hypothetical Cumulatively Degenerative Cycle
co-acting with the Vicious Cycle of Poverty,
and centered upon the Human Reproductive Cycle,
as Primary Cause for the Civilization Diseases"

The study not only accounts for

- (1) The large differences in the incidence of diseases when primitive peoples are being compared to peoples living in Western Civilization

but it also satisfactorily accounts for several other correlates hitherto unexplained, e.g.

- (2) The differences in the incidence of diseases when people living in an urban environment are compared to those living in a rural environment.
- (3) The high incidence of many diseases when those of lower social class (Class IV) are being compared to those of high social class (Class I, II).
- (4) The greatly increased incidence of diseases, within as little as one or two generations, when primitive peoples migrate to an urban environment.
- (5) Gradients of disease incidence running in a North-South direction, with the higher incidence in the North falling off towards the equator.
- (6) Gradients in an East-West direction across continents for some disorders.
- (7) The higher incidence of certain diseases amongst peoples borne in winter compared to those borne in summer.

- (8) The occurrence of many of the diseases of civilization amongst juveniles and infants, i.e. juvenile counterparts of diseases in adults.
- (9) The occurrence of certain abnormal conditions even in young infants, e.g. three-month colic, convulsions, head-banging, etc.
- (10) Epidemiologic location of certain diseases within certain areas of cities, e.g. mainly in slum areas, or alternately mainly where certain types of housing predominate, etc.
- (11) The conspicuous absence of certain sensory defects amongst primitives, e.g. their perfect vision into old age, the absence of the susceptibility to motion sickness, the absence of early childhood autism, etc.
- (12) Disease-free ageing of primitives, e.g. freedom from rheumatism, senility, etc.
- (13) Explanation of very many correlates for diseases which have been recorded in the medical literature but which so far have remained unexplained, with the facts now falling together like pieces of a jigsaw puzzle.
- (14) An explanation for the phenomenon of anticipation of disease, with certain diseases occurring at an earlier age in each successive generation.
- (15) The steadily increasing incidence of certain diseases with each successive generation.

How these facts can all be accounted for from the single theory is too lengthy to be detailed here. Shortly, the correlates which tie up with the complexly interrelated factors in the modern-day infant care are those which via physiological intermediates recur in a meaningful relation to the disease correlates, not in a simple cause and effect relationship, but through a whole complex process that shapes itself in time.

Conclusions

The most important conclusion from the work is that the so-called 'diseases of civilization', or more specifically the constitutional predisposition towards the diseases of civilization, should be preventable by making appropriate modifications in certain aspects of our modern-day methods of infant care, e.g. by recreating certain aspects of the primitives' methods of infant care in a modernised form within the modern environment. To this end a programmable, computerised baby sitter has been designed and a mock-up constructed. The idea is to try and simulate the conditions of the baby actually being carried by the mother, so rectifying amongst other things the stimulus-induced development of the nervous system and sensory systems, restoring the waking stimuli to counterbalance the overdeveloped sleep mechanism of the young infant, normalising the pacing of the biological clock, re-aligning the spinal column with the gravitational field instead of it being at right angles to it so normalising amongst other things the piezoelectric effects in bone development, increasing the proportion of growth and development of the brain during a state of wakefulness as opposed to development during a sleep state which otherwise might give a different end result, etc.

Rectification of various other factors in infant care have also been considered in detail.

As an evolutionary surprise we may find that what appears to be a genetic load of hereditary diseases on mankind, might instead to a large extent be a load of degeneracy-induced mutations (DIM) being constantly replenished, and that once the source of the physiologic degeneracy had been corrected (i.e. by way of suitable modifications in the methods of infant care and in the modern environment) these apparent hereditary diseases will in time be eliminated by the processes of Natural Selection, returning man to his Stone Age supremacy of health.

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

June 25, 1991

MEMORANDUM FOR ALLAN BROMLEY

FROM:

D.A. HENDERSON

SUBJECT:

REQUEST FOR MEETING ON EUONTOGENETICS

Mr. Sondorp's thesis is basically that were we to return to a hunter-gatherer society -
-we would do away with breast cancer, assure perfect vision to old age and generally
be far healthier than we are now. There is good reason why none of this work has so
far been published! Nice name -- "euontogenetics"!

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9121626
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

FROM: KISSINGER, Candice: BIOANALYTICAL SYSTEMS, INC.

TO: Dr. D. Allan Bromley

DATE OF
CORRESPONDENCE: 05/21/91

SUBJECT: THE PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON
MICRODIALYSIS. RE: ITS INTEREST TO BRAIN RESEARCH.

DIRECTORATE STAFF
ASSIGNED: ASSIGNED:

ACTION STAFF
REQUIRED: ACTION:

SENDER'S DUE DATE:
OSTP DUE DATE: STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

COPIES TO: D. Allan Bromley
LIFE SCIENCES

WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS:

OSTP RECEIVED: 06/04/91 FILE: P LIFE SCIENCES
DEPT RECEIVED:

9121626

May 21, 1991

RECEIVED

BAS
2701 Kent Ave
West Lafayette
Indiana 47906

D. Allan Bromley
Presidential Science Advisor
Executive Office Building
Washington, DC

91 JUN 4 AIO: 44

OFFICE OF THE
DIRECTOR

Dear Mr. Bromley:

The May 10, 1991 issue of Science magazine listed you as coordinator of the "Decade of the Brain" activities. I thought you might be interested in the proceedings of the recently completed International Symposium on Microdialysis (May 15-17, Indianapolis). Among the speakers were scientists from several federal agencies as well as numerous federal grant recipients. All of them gratefully acknowledged the sources of their funding.

Microdialysis is of particular interest to brain research since it provides the means of monitoring specific neurochemicals in the extracellular space of the conscious, living brain. The technique involves implantation of tiny dialysis probes into specific brain regions. Fluid is continuously pumped through these probes and collected. Any molecule that can diffuse across the membrane can also be collected and analyzed. Microdialysis provides researchers with the means to watch the neurochemical response of small regions of the brain to events such as epileptic seizure, self-administration of narcotic drugs, various behaviors, ischemia, and other events. Unlike current advances in imaging which tend to provide a broader picture of general brain activity, microdialysis can focus in on very small brain regions and specific neurochemicals such as amino acids, acetylcholine, catecholamines, purines, lactate, serotonin, etc. More importantly, the cost of such instrumentation is low, making the technique accessible to most scientists.

I have enclosed two books of abstracts, one from this year's meeting and another from the first meeting in 1989. These will provide you with an overview of the applicability of this technique to brain research. You will note that microdialysis is also being used for research into other body organs. Microdialysis products were first introduced by our company at the Society for Neuroscience annual meeting in Dallas, 1985. We feel confident that this technique will contribute substantially to the advances predicted by the "Decade of the Brain".

Sincerely,



Candice Kissinger
Symposium Coordinator

Telex: 276141
(317) 463-4527
Bioanalytical
Systems, Inc

CURRENT SEPARATIONS

Vol. 9, No. 5
Bioanalytical Systems | May 1989



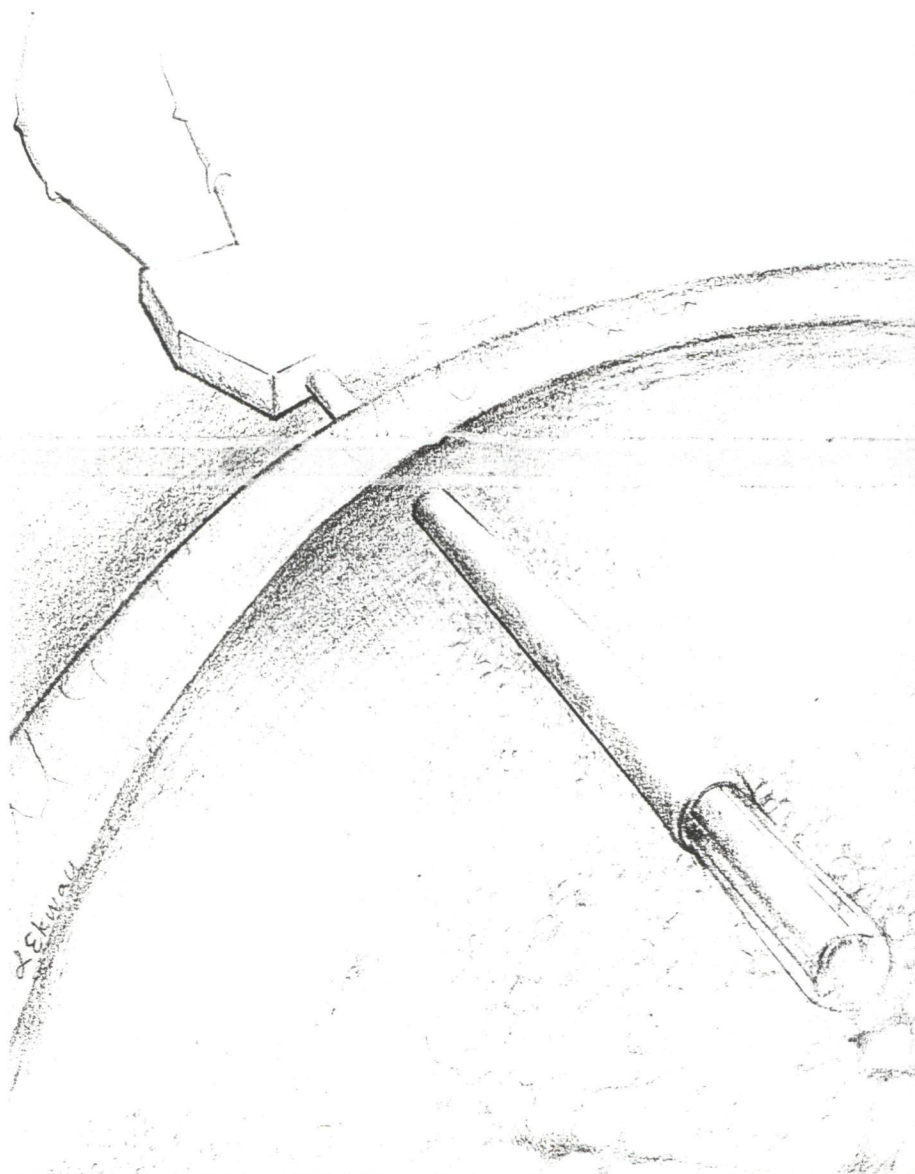
2701 Kent Ave
West Lafayette
Indiana 47906

Candice Kissinger
Microdialysis
Product Manager

FAX (317) 497-1102
TEL (317) 257-4820
TELEX 276141
(317) 463-4527
Bioanalytical
Systems, Inc.

CURRENT **SEPARATIONS**

Vol. 10 No. 3
Bioanalytical Systems/May 1991



**1991 Symposium on Microdialysis
and Allied Analytical Techniques**

"LIFE SCIENCES (CORRESPONDENCE TRACKING)"

TYPE: ACTION DOCUMENT NUMBER: 9121516
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

FROM: HALBERG, Franz and Earl Bakken: CHRONOBIOLOGY LABORATORIES

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 05/20/91

SUBJECT: REQUEST TO MAKE THEIR CASE TO PRESIDENT BUSH, RE:
HEALTH EDUCATION; THE USE OF COMPUTER SYSTEMS FOR
THE STUDY OF CHRONOME, ECT.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED: LIFE SCIENCES

ACTION STAFF
REQUIRED: FOR DAB SIGNATURE ACTION: Direct Reply

SENDER'S DUE DATE:
OSTP DUE DATE: 06/10/91 STAFF DUE DATE 06/10/91
DATE COMPLETED: DATE COMPLETED/DEPT: 05/31/91

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS: Damar changed the action on this from Bromley signature to
Direct Reply by DLS on 05/30/91.

OSTP RECEIVED: 05/28/91 FILE: P- LIFE SCIENCES
DEPT RECEIVED: 05/30/91

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

May 31, 1991

Dear Dr. Halberg:

Thank you for your interesting letter on chronobiology. Biologic rhythms are certainly a fact of life. How effective their analysis and modulation might be in promoting better health is worthy of careful study.

As I am sure you must be aware, the President's schedule is a very full one, indeed, and could not accommodate such a presentation as you propose. Might I suggest instead that you approach Assistant Secretary for Health James Mason as it is his office which bears principal responsibility for health promotion programs.

Sincerely yours,

A handwritten signature in cursive script that reads "Rachel E. Levinson".

Rachel E. Levinson
Assistant Director for Life Sciences

cc: Dr. Bakken

Dr. Frank Halberg
Director
Chronobiology Laboratories
University of Minnesota
420 Washington Avenue, S.E.
Minneapolis, Minnesota 55455

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

May 31, 1991

Dear Dr. Bakken:

Thank you for your interesting letter on chronobiology. Biologic rhythms are certainly a fact of life. How effective their analysis and modulation might be in promoting better health is worthy of careful study.

As I am sure you must be aware, the President's schedule is a very full one, indeed, and could not accommodate such a presentation as you propose. Might I suggest instead that you approach Assistant Secretary for Health James Mason as it is his office which bears principal responsibility for health promotion programs.

Sincerely yours,

A handwritten signature in dark ink, reading "Rachel E. Levinson". The signature is fluid and cursive, with a long horizontal flourish extending to the right.

Rachel E. Levinson
Assistant Director for Life Sciences

cc: Dr. Halberg

Dr. Earl Bakken
Chairman, Advisory Board
Chronobiology Laboratories
University of Minnesota
420 Washington Avenue, S.E.
Minneapolis, Minnesota 55455

9121514

Chronobiology Laboratories University of Minnesota

Director: Prof. Franz Halberg

May 20, 1991

Dr. D. Allan Bromley
Assistant to the President
for Science and Technology
Office of Science and Technology Policy
Rm. 358 Old Executive Office Bldg.
17th St. and Pennsylvania Ave. N.W.
Washington, DC 20506

RECEIVED

91 MAY 28 A 9:25

OFFICE OF THE
DIRECTOR

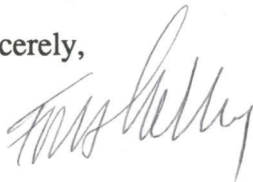
Dear Dr. Bromley:

The American health care system this year, at an estimated cost of \$660 billion, may include 25% of expenditures related to a defensive medicine; 20% related to the bureaucracy of reimbursement and cost control, and 10-15% for regulation. Self-help whenever possible certainly is an objective for reducing cost, since one can hardly sue or bill oneself, nor does one need a license if properly taught. This brings us to the matter of education. We advocate the use of computer systems for the study of the chronome, our time structure of biologic rhythms and trends, as reference standards for the quantification of health and personality and the recognition of elevated disease risk that can prompt risk lowering for health improvement; a small investment into this chronobiologic technology can go a very long way in cutting health care costs while improving rather than compromising on quality, as is usually considered in connection with cost reduction in mainly curative health care. We want to go via the path on the right rather than that on the left of Figure 1 on the next page. By joining educative chronobiology and chronobioengineering for action early in life when an elevated disease risk is still reversible, Mr. Bush could become a true health via education president.

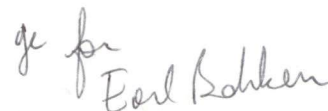
We would appreciate an opportunity to make our case to President Bush in your presence. In the interim, we thank you for any consideration. We enclose some documents that reveal what we are doing, and indicate a current problem. We are more concerned, however, with the broad scope of action in achieving chronobiologic health literacy, in the context of Secretary Mason's 'Prologue to Action' and beyond.

Thanking you for your consideration,

Sincerely,



Franz Halberg
Director, Chronobiology Laboratories
University of Minnesota



Earl Bakken
Founder and Director, Medtronic Inc.
Chairman, Advisory Board
Chronobiology Laboratories
University of Minnesota

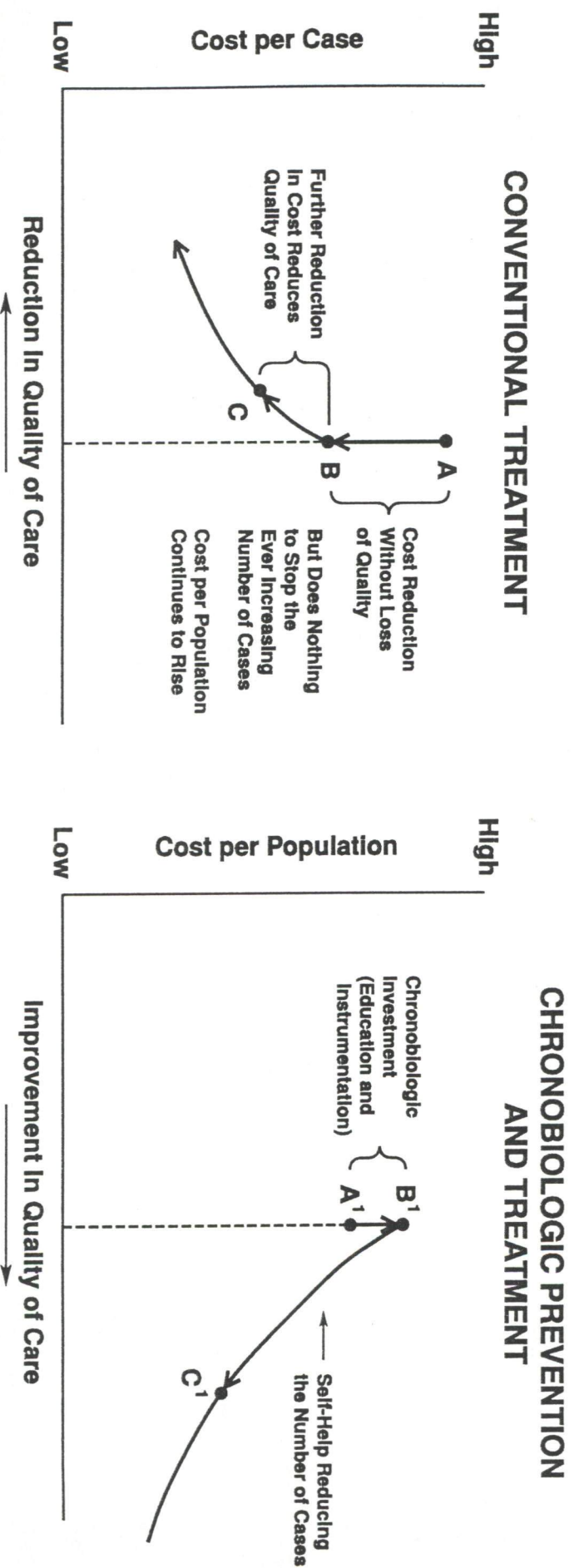
FH/ms

P.S: Some materials follow by mail.

University of Minnesota, Chronobiology Laboratories, Department of Laboratory Medicine and Pathology
☐ 5-187 Lyon Laboratories, 420 Washington Avenue S.E., Minneapolis, Minnesota 55455, USA
© (612) 624-6976 • Fax (612) 624-9989 • Telex 5106013001

COST AND QUALITY TRADE-OFFS CONCERNING HIGH BLOOD PRESSURE AS A FIRST AREA FOR CHRONOBIOLOGIC LITERACY FOR PREVENTIVE SELF-HELP IN HEALTH IMPROVEMENT (RIGHT)

VS. TREATMENT ONLY (LEFT)*



* Adapted from: W.B. Stason: Economics in Hypertension Management: Cost and Quality Trade-offs. *J. Hypertension* 5 (Suppl 1): S55-S59, 1987. See also W.B. Stason: Cost and Quality Trade-offs in the Treatment of Hypertension. *Hypertension* 13 (Suppl 1): I-145, I-148, 1989; National High Blood Pressure Education Program Coordinating Committee: National High Blood Pressure Education Program Working Group Report on Ambulatory Blood Pressure Monitoring. *Arch. Int. Med.* 150: 2270-2280, 1990. Jesse M.J., Weissler A.M., chairpersons: Workshop I: Quality of cardiologic care in the era of cost containment. In: A Symposium: Cost Containment Issues in Cardiology, January 25-27, 1985, Tucson, Arizona. *Am. J. Cardiol.* 56: 62C-64C, 1985.

ROUTING - REQUEST

Please



READ



HANDLE



APPROVE

and



FORWARD



RETURN



KEEP OR DISCARD



REVIEW WITH ME

Date

5/21/91

From

Dr. Franz Halberg

To Dr. D. Allan Bromley

Ref: Letter dtd
May 20, 1991

Document Originally
Attached to
Following Page

Blood Pressure Assessment in a Broad Chronobiologic Perspective

F. HALBERG, E. BAKKEN, G. CORNÉLISSEN, J. HALBERG, E. HALBERG, and P. DELMORE
Chronobiology and Medicine

Chronobiology deals with the rhythmic patterns that occur in all forms of life [1-5, 7-32, 34-37, 39-43]. Virtually all organisms exhibit approximately daily (circadian) cycles. In human beings, prominent rhythms are found in blood pressure, circulatory pulse, body core, and surface temperature and in chemical variables of blood, urine, and tissues. The medical section of this new science explores the relationships of rhythms to prediction, prevention, diagnosis and treatment of diseases. Several decades of research worldwide have established that medical diagnoses can be subject to a much higher proportion of false positives (e.g., "office hypertension") and false negatives (e.g., "odd-hour" hypertension) when only single samples are taken at arbitrary times of the day instead of taking rhythms into account. Radiation, chemotherapy and other treatments have been shown to have markedly different efficacy and safety depending upon the pattern of administration within the day. Without engineering tools, chronobiology had to rely on manual-measurement series that were cumbersome to collect and required methods of analysis that were not generally available. Modern bioengineering with microcomputers can bring the findings of chronobiology on circadian and other rhythms into the mainstream of medicine. Chronobiology can thus provide new dimensions to health care.

Medicine stands on the threshold of a new era in prevention as well as diagnosis and treatment, based on the combination of several emerging engineering technologies with an understanding and application of the health effect of life's rhythms. Through chronobiologic programs, modern engineering technologies can lead to:

- The large-scale use of portable, personal long-term ambulatory monitors of biologic variables such as blood pressure, pulse, the ECG or EEG, variables that undergo large, spontaneously and reactively recurrent changes
- The availability of data base systems to acquire and analyze the considerable volumes of data obtained from personal monitors
- The availability of statistical procedures to analyze and model the biologic rhythms and from them to devise optimal-dosage time patterns for specific individuals
- The availability of portable, programmable devices to administer therapy, e.g., by physiologic rate-adjusted cardiac pacemakers or drug pumps.

The routine employment of chronobiologic methods in medical screening, diagnosis, prognosis, treatment and, most important, disease prevention, remains the challenge to be met.

The importance of chronobiology in medicine is herein illustrated in the context of blood pressure, even if recent debates revolving around measuring cholesterol [38] may also benefit from a chronobiologic approach [28, 29, 42]. More than half of the serious disease and death occurring in middle-aged people is linked to behaviors that can be changed or health conditions that can be prevented or treated. Three very important examples are smoking, a diet high in saturated fat, and high blood pressure.

Blood Pressure Measurements that miss the Chronobiologic Point

As an example for the application of chronobiology, health assessment of an individual need not rest only on a visit to the clinic. Visits are currently scheduled at a time convenient to both patient and physician, without taking into account the great variations that occur in all of our physiologic variables over a 24-h period and over a weekly period and even a monthly and yearly period. Since quite large variations take place in human blood pressure over 24-h periods, chronobiology as the study of the parameters of biologic variation in relation to time is particularly pertinent to our way of handling blood pressure [3, 13, 19–22, 24, 25]. Indeed, at present (non-chronobiologic) blood pressure screening is usually offered according to the recommendation of the World Health Organization (WHO) and on only some occasions by the use of 24-h ambulatory cardiovascular monitoring.

Most health professionals and most of the broad public ask only: What is your blood pressure? Official convention focuses upon "the" blood pressure, relying on casual measurements. Such measurements are recommended, among others, in the WHO Guidelines [6, 44, 47]. For a test of a mild blood pressure elevation (90–104 mm Hg diastolic), without organ damage and "to provide a safe classification of patients," the International Society of Hypertension joins WHO in recommending the criterion of the average of 2 (casual) diastolic measurements. If the average of these is 90 mm Hg or above, further measurement pairs on at least two further days over four weeks are recommended. If the average values of these are above 100 mm Hg, drug treatment is to start. If in turn these means are below 100 mm Hg, further measurements over 3 months and behavioral intervention, but not drug treatment, are recommended. If the overall average is now above 95 mm Hg, drug treatment is recommended; if the average is below 95 mm Hg, behavioral intervention is prescribed with further observations over 3 months. It is left to the individual to pick the time of measurements.

Implicit in the foregoing convention are the assumptions that (a) variations in blood pressure and heart rate are the effect of changes in posture, responses to meals, exercise or other stimuli, emotional or physical, and that (b) a short span of sitting or lying down of, say, five minutes or so, in the setting of a medical office, is a better standardization than no standardization whatsoever, in order to somehow "control" the stimuli of daily life and thus to approximate the (true) blood pressure.

The recommendation of 24-h ambulatory blood pressure and heart rate monitoring as such exploits the availability of new monitors only and does not take full advantage of the data in the light of chronobiologic facts. Assumption (a) above is the excuse for refraining from a consideration of the dynamics of blood pressure. These continue to be regarded as trivial effects of changes in posture, notably exercise and other stimuli. With most ambulatory monitoring instruments, it remains necessary to stop what one does physically during the actual measurement, but with this qualification, assumption (b) is changed into endeavor (c), namely into the aim of obtaining a reflection of average pressure in "real life" by a 24-h and perhaps also by a daytime and nighttime average pressure. Since all variations are treated as responses to external stimuli, one does not do much if anything about them, except perhaps for asking that changes in posture, meals, etc., be recorded. In debates about nonchronobiologic ambulatory 24-h records versus casual measurements, it should be realized that both approaches present serious shortcomings. Built-in rhythms and their characteristics such as a measure of the extent of a regular 24-h change (circadian amplitude) and of the timing of high values (acrophase) are ignored. Definitions of some rhythm characteristics are provided in Fig. 1. That three of these characteristics of heart rate are partly inherited is shown by studies on twins reared apart [26]. Indirect evidence for the endogeneity of the human heart rate and blood pressure rhythms is available from their free running with natural periods differing from environmental ones in social isolation [2] and under certain other conditions [16]. The fact is also demonstrated that responses to external stimuli (i.e., the blood pressure change in response to the immersion of the hand in cold water [23] or simply reading aloud) depend upon the stage of partly endogenous circadian rhythms.

The cost effectiveness of nonchronobiologic 24-h ambulatory monitoring has been scrutinized thus far without considering what can be learned from the spontaneous and reactive blood-pressure and heart-rate dynamics. The investment into new machines has not been accepted as justified on the basis of an improved 24-h average or of averages for fractions of the day, such as the waking, sleeping or other spans. Thus far, the health profession's response has been guarded. Whatever their data source, whether they rely upon conventional, manual, or ambulatory automatic measurements, most health care personnel continue to act according to what "the (or the average)" blood pressure of a given person is. This inquiry only into the or the average blood pressure is insufficient when a more reliably defined mean and added dynamic information can be extracted from the same record. There is indeed another alternative to the WHO guidelines [6, 44, 47], one that adds a new dimension to blood pressure assessment: the chronobiologic approach, as summarized in Fig. 2. The message of this note is that there is a need for chronobiologic monitoring in order to improve the sensitivity of screening, the reliability of diagnosis, the accuracy of prognosis and the timing and efficacy of treatment. But first and foremost, there is a need to emphasize approaches for the prevention of high blood pressure.

Blood pressure chronobiology focuses upon both the predictable and the global dynamics of the variation in blood pressure that is likely to be missed if one measures at only one or another convenient time of day. As in the case of the 24-h profile, some treated or untreated cases of high blood pressure show elevations at times when casual measurements are not taken as a rule, as for instance during odd hours or sleep (Fig. 3) [25]. To detect such cases, systematic manual or preferably auto-

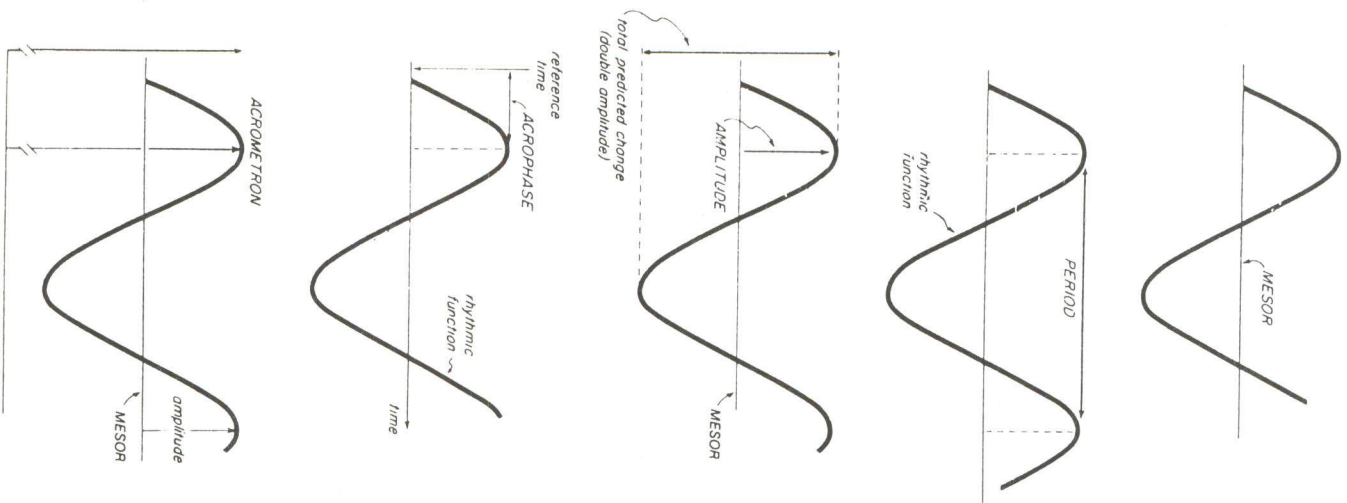


Fig. 1. Definition of Rhythm Characteristics
MESOR, rhythm-adjusted mean (Midline-Estimating Statistic Of Rhythm), defined as average value of rhythmic function (e.g., cosine curve) fitted to data; expressed in same units as original data. Note that MESOR will differ from arithmetic mean if data are unequidistant (e.g., concentrated near crest of rhythm) and/or cover non-integral number of cycles; PERIOD, duration of one complete cycle in rhythmic function; expressed in time units, such as seconds, hours, days or years, or in physiologic units such as complete cardiac, respiratory or menstrual cycle; equated to 360° for angular expression of acrophase; AMPLITUDE, half of total predictable change in rhythm, defined by rhythmic function fitted to data; expressed in original or "relative" units, e.g., as percentage of series mean or MESOR; ACROPHASE, lag from reference time of rhythm's crest-time, defined by rhythmic function fitted to data; usually expressed in (negative) degrees, with $360^\circ \equiv$ period, 0° = reference time; customary time units (e.g., clock-hours and minutes, days, weeks, months or years) or physiologic units (e.g., number of heart beats, respiratory or menstrual cycles) also appropriate for rhythm synchronized with corresponding period; ACROMETRON, highest predicted value taken by rhythmic variable, i.e., the sum of the amplitude and MESOR

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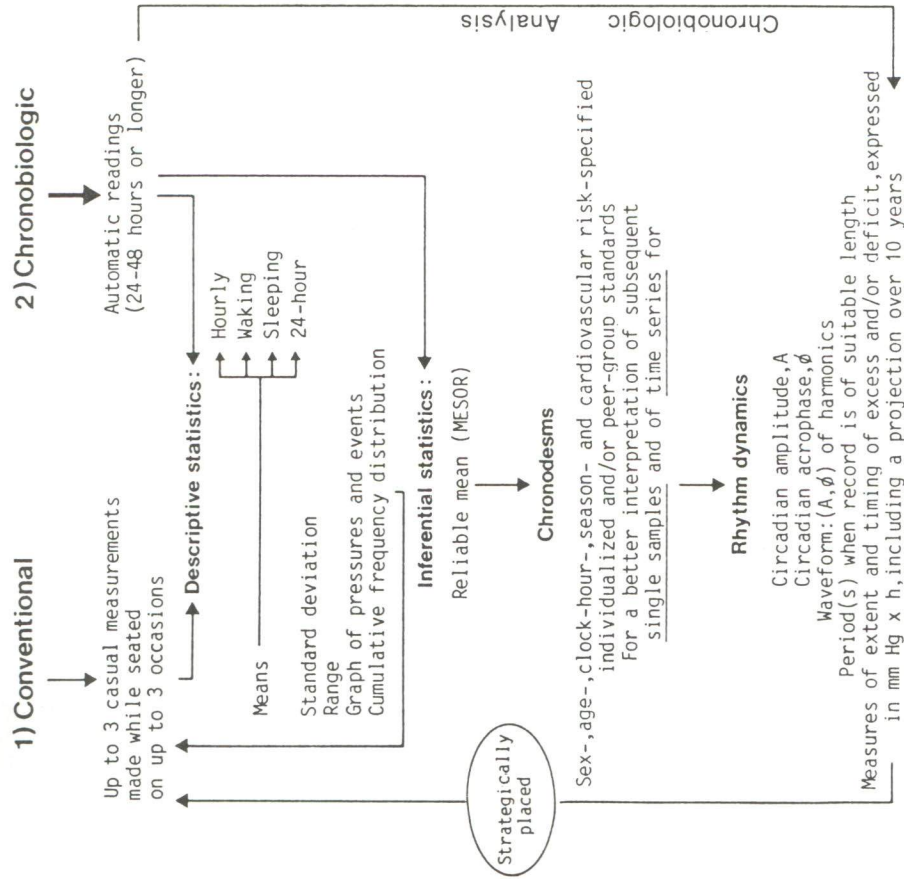


Fig. 2. Scheme indicating that the chronobiologic approach includes descriptive and inferential statistics. Chronobiologic around-the-clock monitoring yields several kinds of chronodesms. Some of these are time-specified reference limits for the interpretation of strategically placed (rather than casual) measurements. Other reference standards, paradigms, serve for interpreting the MESOR; amplitude, A; acrophase, ϕ ; and periods, τ , separately or jointly as features of the quantified dynamics of time series

matic around-the-clock measurement is required. Chronobiologic evaluation also reveals that a 24-h profile does not suffice for a first screen. Thus, in a majority of cases, statistically significant differences are found in the 24-h average of two 24-h profiles repeated within a few weeks, even when each profile is based on relatively dense (7.5-min) measurements. A 48-h average, more reliable than the 24-h average, is not the sole and not necessarily the major merit of the chronobiologic approach. An important point in the chronobiologic approach is the need to start any screening with around-the-clock measurements rather than carrying out such a monitoring profile only in the case of a suspicion of deviant blood pressure. The contribution by chronobiology, however, is the ability to account for a usually large circadian variation, encountered over 24 h under ambulatory conditions in assessing any cumulative

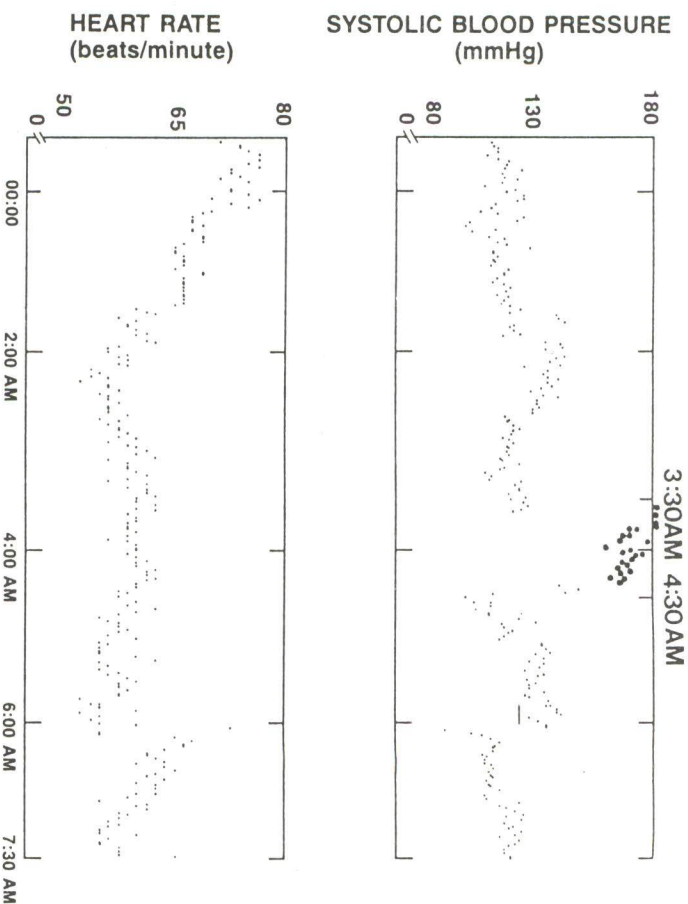


Fig. 3. An unsolved problem: hypertensive episode during sleep without concomitant tachycardia. A marked rise in systolic blood pressure (BP) during the night (*bold face*), lasting for about 50 min, is seen (*top row*), in the absence of corresponding changes in heart rate (*bottom row*). This fact suggests that the changes in blood pressure are not due to changes in movement. In the absence of a concomitant electroencephalographic tracing, one can only speculate as to whether the subject had a panic episode in a dream. If indeed he dreamt, one would also have to account for the mechanisms that under certain conditions, in a dream, bring about an increase in BP and under others a decrease in BP, as observed during another sleep episode [25] on the same subject (not shown). Whether the changes noted, the hypertensive episode in particular, are related to the medication (*nardil*) which the subject took, must be explored. The changes in BP may reflect states of mind of interest to those concerned about brain-heart interactions. The 2325 values per variable monitored on this man (not all shown) allow the isolation in his BP spectrum of 1.6- and 1.8-h components. Certainly, the data during the episode exceed the range of change usually encountered for BP ultradian. The 50-min duration of the episode is in keeping with the possibility that it is an exacerbation lasting for half the duration of an underlying ultradian (~1.7-h) rhythmicity. Such episodes would not be detected by sole reliance upon daytime measurements. The episode may pose a threat if it is maintained for longer than half of an ultradian cycle (about 50 min), a period actually isolated for this particular subject, and/or if it represents more than an isolated episode in the particular BP series examined.

excess or deficit on the one hand while resolving part of the overall variation as predictably rhythmic and assessing any changes in rhythm characteristics on the other hand.

By the fit of cosine functions with periods of 24 h and submultiples thereof, computer software resolves the characteristics of variation, as shown in Fig. 1. Chronobiologic methods can be applied to measurements taken manually, with a sampling

Summary and Conclusions

The diagnosis and treatment of deviant blood pressure can be undertaken with greater accuracy and higher success if one uses the "dynamic" characteristics of the pressure rather than just the present "static" viewpoint based primarily on an average pressure. In lieu of sole reliance upon repeated casual measurements, as recommended by WHO, and also in lieu of the inspection only of records from automatic 24-h monitoring, we advocate a third alternative, namely a chronobiologic exploitation of data collected systematically. These can be obtained by traditional sphygmomanometers or by means of automatic monitoring devices. Modern ambulatory monitors become cost-effective once the merit of chronobiologic endpoints, such as a measure of excess or deficit, each assessed in relation to time-varying limits derived from peer groups, is recognized. The information obtained by additional endpoints describing the extent and timing of change, all presented in a computer-prepared profile over time, the sphygmochron, is documented by illustrative examples and by reference to a more detailed presentation and bibliography. Indications for the use of the chronobiologic approach to blood pressure evaluation are also succinctly presented. By these examples from the field of blood pressure evaluation, we have tried to document the need for awareness of the broader scope of the science of physiologic variation in relation to time: chronobiology, for medical practitioners as well as researchers.

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by the social regimen. Our getting up and going to bed at the times set by society each day reset our free-running internal rhythm setters into step with worldtime. The brain (or mind) is therefore a vital link in the time region's coordination of the heart, the rest of the cardiovascular system and the whole person. Looking at all biological variables with a chronobiologic viewpoint will greatly enhance diagnosis, therapy and prevention in nearly all facets of medicine, but the application to blood pressure can be used already now with great service to the quality of life for many patients.

The chronobiologic view is that circadian and other rhythms are endogenous components that are synchronized by physicochemical as well as socioecologic factors. The existence of an underlying intrinsic rhythmic mechanism is supported by the observation that blood pressure rises before awakening and cannot thus result only from a change in posture or activity [7, 25, 43]. It was also shown that the circadian amplitude in blood pressure decreases only slightly under conditions of bedrest [25, 35]. Halberg in 1953 [7a] documented the phenomenon of an activation of both the adrenal cortex and medulla, codetermining a rise in blood pressure prior to awakening.

The adrenal cortex is critical in the interdigitating networks coordinating metabolic and adjusting networks as well as complementary networks for growth, repair and reproduction. The adrenal cortical cycle has been described as the pacemaker of circadian rhythms in circulating blood eosinophil cells and to act at the cellular level upon rhythms in phospholipid labelling and mitosis [34]. The adrenal cycle was shown to persist in the histologically validated absence of the suprachiasmatic nuclei [40].

The persistence of adrenal cortical bioperiodicity in rodents was documented directly by corticosterone determinations after stepwise brain ablation [5] and in vitro [1]. Indirectly, on human beings, the persistence of circadian adrenal periodicity has also been documented by counts of circulating blood eosinophils after hemispherectomy [15], during regressive electroshock [8] and coma [30].

Robel and Baulieu have shown that, apart from the long-known contribution of major steroidogenic glands, dehydroepiandrosterone and its ester sulfate are also made in the brain [37]. These authors also showed that dehydroepiandrosterone undergoes a circadian cycle in the brain, and that following adrenalectomy and orchidectomy in rats, it not only continues to be found, but continues to exhibit a circadian rhythm in the brain [36]. These results support the hypothesis for the existence of an autonomous cerebral mechanism coordinating the production of $\Delta 5\text{-}3\beta\text{-hydroxysteroids}$. It is also pertinent to note that the acrophase of pregnenolone in brain precedes, with statistical significance, the acrophase of corticosterone in rats [45], as does the acrophase of dehydroepiandrosterone in plasma. Moreover, in the rat, the circadian rhythm of corticosterone, pregnenolone and dehydroepiandrosterone are in phase between their variation in plasma and brain. This is not the case for the adrenal phase relations in humans, the rise of cortisol preceding that of dehydroepiandrosteron-sulfate by about 6 h [17]. The differences in phase relations between the two kinds of steroids observed between the two species (rodents and human beings) describe internal phase relations and are therefore independent of the difference in the rest/activity cycle between the two species. These differences may result in part from a modulatory effect exerted by the CNS. The pineal gland is a logical candidate to intervene in such a coordinating mechanism by means of its feedsideward action [34].

schedule shown to be useful for a given purpose and adopted with a discipline that has to be taught in the context of early formal as well as adult education. The use of presently available modern automatic, fully ambulatory recording systems, however, greatly facilitates data collection and, in combination with proper software, renders the chronobiologic approach to blood pressure variation much more practical than reliance only upon a few casual measurements.

Methods

If one measures any of the body's physical variables continuously or at frequent intervals around the clock (preferably for at least two days), the plotted data invariably show rises and falls that have an obvious 24-h periodicity. By submitting these data to mathematical analysis, one can pull out the fundamental frequency and plot it as a sinusoidal function. The cosine curve can be used for convenience. From this plotted cosine, one can see the amplitude of the fundamental variability and the timing of the peak(s) and valley(s) and can also plot the midline for the variability. These mathematically calculated features are often sensitive indicators of present or potential disease that cannot be found in a few casual measurements, e.g., of blood pressure and heart rate, taken at an arbitrary time in a physician's office. In many cases, this chronobiologic approach yields meaningful information when casual readings do not.

Hardware

Until recently, the taking of blood pressure readings every 10 min or so around the clock has not been clinically practical. Now, however, automatic blood pressure recording equipment has become available. Smaller and smaller wearable equipment for fully ambulatory recording is being developed [25]. Apart from the nearly noiseless and hence less sleep-disturbing miniaturized ambulatory monitor, manufactured by Colin Medical Instruments (Japan), now extensively used by us and others, perhaps the ambulatory monitors most widely used today are the Pressurometer III (Del Mar Avionics, USA); the Ambulatory Blood Pressure Monitor (Instruments for Cardiac Research, subsidiary of Squibb, USA); and the Acutracker Model 103C (Oxford Medilog, USA). In their present form, the large-scale, long-term use of these monitors is difficult and costly. The Pressurometer demands the placement of electrodes that are a nuisance for the patient and, after long-term use, may cause skin rashes; the Squibb instrument requires frequent battery changes; and the Colin Medical Instrument requires CO_2 cartridges. There are also limitations in terms of data storage in solid-state memory, although the Colin Medical Instrument holds over 600 measurements that can easily accommodate more than one week of data with a sampling interval of 30 min. This kind of equipment begins to give us data that represent real life and take into account what happens to the blood pressure during most of the range of life experiences from different stages of sleep to various kinds of experience in wakefulness on weekends as well as weekdays.

Recordings over at least 48 h and preferably a week show the effects of emotional, physical and *time* impactors that cannot be assessed in single readings, as, for instance, the episodes of relatively high or low pressure occurring during sleep (Fig. 3) [25]. During one night, the blood pressure rose for ~50 min, without a concomitant change in heart rate. In another night, in the same subject [25], an episode of a relatively low blood pressure occurred.

It is important to know the duration of episodes of such hyper- or hypotension and what their extent might be, whenever they occur. A chronobiologic approach is particularly rewarding when it uncovers events that are not seen in casual measurements.

Analyses

A chronobiologic blood pressure assessment relies on both parametric and non-parametric approaches. For either approach, the reference standard is derived from data of living age- and sex-matched peers rather than solely from the tombstones of a previous generation. When time-varying reference limits are unavailable as yet, excess can refer to the sum of the circadian amplitude and the rhythm-adjusted mean or MESOR. This sum, the acrometron, is based upon around-the-clock sampling on healthy peers and is thus preferred to an arbitrary limit such as 140 and 90 mm Hg for systolic and diastolic blood pressure, respectively. The reference limits used here are derived from only 39 clinically healthy ambulatory North American men, each monitored at 7.5-min intervals for 24 h. This sample size of a reference standard will be replaced by one based on several hundred already available series obtained by noninvasive 24-h monitoring at 7.5- or 10-min intervals. The recommended monitoring span has now been extended to a minimum of 48 h. Hence, reference standards based on 48-h samples are needed, as are reference standards for "skeleton" sampling [25], namely for uninterrupted sampling every 10 min during sleep with interruptions during wakefulness, implemented with an automatic oscillometric room-restricted Nippon Colin machine.

Sphygmochrons: Monitoring Profiles over Time for Comparison with Peers

Special forms have been designed to report the blood pressure status of patients chronobiologically. These forms focus on circadian features of blood pressure variability, such as the MESOR, amplitude and acrophase (Fig. 1). In addition, indices of blood pressure excess (or deficit) are evaluated by comparing the patient's own record with the characteristics of healthy peers. These forms assist in the proper detection and treatment of patients and can be used as a convenient tool in clinical practice. This data summary chart, developed by us, has been dubbed a *sphygmochron*, a blood pressure and heart rate monitoring profile over time [25]. It represents a computer comparison of a person's data with clinically healthy peer group limits. These sphygmochrons describe a number of chronobiologic characteristics that result from an approach summarized in Table 1.

one seeks to recognize the risk of deviant behavior (e.g., of blood pressure), both early and in a time-dependent fashion to prompt preventive action. When such methods are applied to MESOR- or amplitude-hypertensive patients, they serve to assess their response to treatment.

The sphygmochron presents, illustrates and interprets the circadian rhythm characteristics of blood pressure and heart rate. When many measurements are taken around the clock, one likely finds values above or below reference limits, not only the fixed limits recommended by WHO, but also outside chronobiologic limits, the so-called chronodesms. In addition to providing an estimate of such deviant single values, the sphygmochron also addresses new and more pertinent questions such as "How long does blood pressure remain above a given time-varying threshold?", "To what extent does the blood pressure exceed the threshold at a given time?", "What is the total excess and its projection over a lifetime?" and "When does most of the excess occur?" On this rational basis, treatment can be timed more appropriately and its effects can be objectively monitored and tested statistically, not only on a population basis, but also for the given individual. In summary, characteristics of rhythms and of blood pressure excess (or deficit) serve several purposes:

1. To initiate treatment if needed
2. To time treatment when it is most effective and least harmful in terms of undesired effects
3. To help in prognosis and diagnosis with a better assessment of health status
4. To screen for early recognition of risk before disease sets in, so as to intervene by preventive measures such as exercise, diet or other nondrug treatment.

We are at the threshold of a constructive evolution in medicine, in particular with respect to blood pressure and heart rate. We recognize variability, not as a foe to medical diagnosis and treatment, but as the source of information to be extracted by special hardware and software for use in a refined screening and prevention as well as diagnosis and cure. Automatic recorders are available at a cost that will decrease as their use increases. Algorithms analyze dense and long records for dynamic characteristics. Accumulating evidence from the use of modern hardware and software reveals the health effects of rhythmic changes and some of their mechanisms. Rhythm characteristics include a better mean, the MESOR, than that of one or a few casual measurements. Additional rhythm and trend characteristics complement traditional means, ranges and standard deviations, notably to detect at birth risk of developing civilization diseases later in life.

We believe that the chronobiologic method of blood pressure analysis will lead to more accurate and successful diagnosis and treatment. If large numbers of today's false positives can be removed from therapy and if a substantial percentage of today's false negatives can receive the appropriate treatment, the reduction in morbidity and mortality will be considerable. Getting people into the right treatment category will clearly cut health costs while improving health care for millions.

The chronobiologic component in blood pressure reflects but one end result of the body's coordinating systems that link all the "feedsideward" mechanisms throughout the body into one harmonious symphony. The intermodulating rhythms occur at all levels from the single cell to the whole organism. The synchronization of these changes is done via the central and autonomous nervous system and is influenced

Table 2. Circadian amplitude (A) of diastolic blood pressure (BP) (automatically monitored every 15 min for 48 h on 15 boys and 15 girls with differing family history of high BP), but not mean value, correlates with echocardiographically determined thickness of the interventricular septum

Kind of BP index	Index	All children		Children with PFH ^a of high BP		Does the index work?
		r	P value	r	P value	
Chronobiologic	Circadian A	0.385	0.045	0.672	0.016	Yes
Conventional	Mean value	-0.039	0.840	0.059	0.848	No

^a PFH = Positive Family History [from 4].

A breakdown of family history in terms of paternal or maternal family history of high blood pressure reveals a stronger influence of the maternal family history of high blood pressure on the circadian blood-pressure amplitude of the newborn. The consideration of a family history of diabetes and of pregnancies complicated by an elevated blood pressure and/or the taking of beta-adrenergic drugs and/or corticoids shows alteration of the circadian amplitude. These results suggest the possibility of intervention in utero, for instance by dietary means in pregnancy.

Serial blood pressure measurements provide sensitive indices that focus on blood pressure variability. These features of the time structure evolve rapidly following birth. On the basis of around-the-clock rhythmometry, our work presents several indications of the sensitivity of the circadian blood pressure amplitude not only as a harbinger of cardiovascular disease risk but also as a correlate of target organ involvement. In healthy 14-year-olds, we find that the circadian amplitude, but not the 24-h mean of diastolic blood pressure, correlates with the interventricular septum thickness (Table 2).

Discussion

The uncertainty of an elevated blood pressure is usually discussed on the assumption that blood-pressure variability is mainly due to measurement error, to the patient's posture and to responses to external stimuli. This view disregards the fact that part of the variation in blood pressure is spontaneous and accounted for by rhythms of several frequencies, among which the 24-h (or circadian) rhythms are most prominent. In order to assess the variation in blood pressure, repeated measurements should be taken, preferably at strategically selected times so as to quantify and exploit more reliable mean values and novel dynamic endpoints. Although presently available automatic recorders greatly facilitate data collection, the analytical methodology available as computer software for resolving the characteristics of rhythm can also be applied to measurements taken manually, once a proper sampling schedule is adopted. The methodology offered by chronobiology allows the assessment of the extent and timing of rhythmic change and the establishment of time-varying norms for healthy peer groups and/or individuals. By comparing these dynamic indices of blood-pressure variation of a given individual with those of peers,

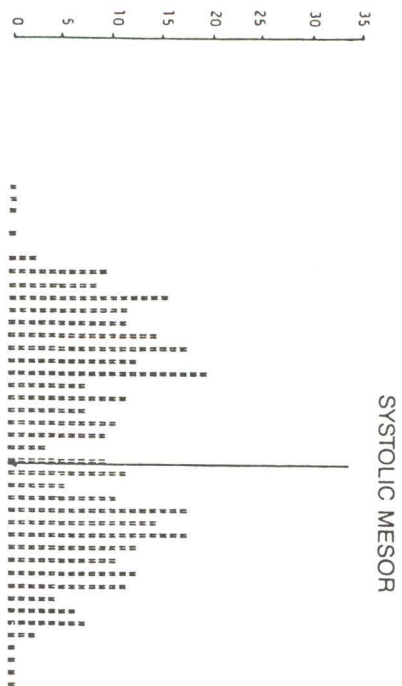
Table 1. Chronobiologic endpoints, e.g., of human blood pressure

1. MESOR, M	Midline-estimating statistic of rhythm, based on systematic sampling, taking dynamics into account; replaces mean of casual measurements at arbitrary times
2. Range, R	total partial, e.g., 90%, 50%, circadian range (e.g., of hourly mean values)
3. Standard deviation, SD	
4. Trends	Intercept and slope of linear trend; coefficients of higher-order (e.g., quadratic or cubic) polynomials
5. Periodicities	Rhythm characteristics, e.g. circadian amplitude, A circadian acrophase, ϕ circadian waveform, (A, ϕ) of harmonics Parameters describing shape of spectrum, e.g., high frequency dominant over low frequency or vice versa
6. Non-periodic, non-trend components	Parameters describing shape of spectrum, e.g., high frequency dominant over low frequency or vice versa
<i>All of the above endpoints may or may not be deviant. Other endpoints, related to cumulative deviation, are:</i>	
7. Excess	short-term: extent: hyperbaric index duration & timing of elevation long-term projection: e.g., 10-year excess
8. Deficit	short-term: extent: hypobaric index duration & timing of deficit long-term projection: e.g., 10-year deficit

Results

When one records blood pressure around the clock, one can observe even larger changes than those that occur from moment to moment both in systolic and diastolic readings. Figure 4 shows the distribution of blood pressures of a clinically healthy woman, ranging systolically from 73 to 153 mm Hg and diastolically from 51 to 91 mm Hg. The overlap between the two distributions is shown as black dots. It may be foolhardy to disregard circadian changes which are as large as the differences Fig. 3 documents. Healthy individuals can have an average dispersion of 60 mm Hg in systolic and 50 mm Hg in diastolic pressure. By submitting these data to a computer program, one can plot not only the time course of the blood pressure as such, but one can also derive characteristics of an approximating curve (consisting of a fundamental such as a 24-h cosine plus a few harmonics). This curve for the individual can then be

Fig. 4. Fully ambulatory automatic monitoring of a clinically apparently healthy woman (EH, age 64 years) reveals a wide range of cardiovascular variability. Questions about the blood pressure (BP) of a patient are rhetorical. The cost-effective recording and interpretation of variation are mandatory. Note bimodal rather than bell-shaped distribution of systolic and diastolic BP of the subject and the large overlap between the two distributions. Hourly averages of data mostly at ~10 min intervals, with interruptions, for 26 days; M, MESOR; A, circadian amplitude; SBP, systolic BP (double dashed line); DBP, diastolic BP (single dashed line); PP, average pulse pressure (PP = SBP - DBP, M).

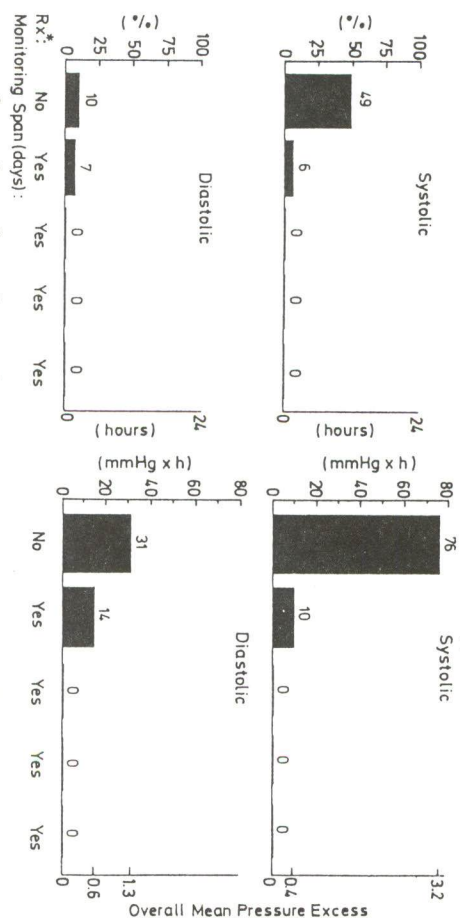


DIASTOLIC MESOR



SYSTOLIC MESOR

Percent Time Elevation



Hyperbaric Index

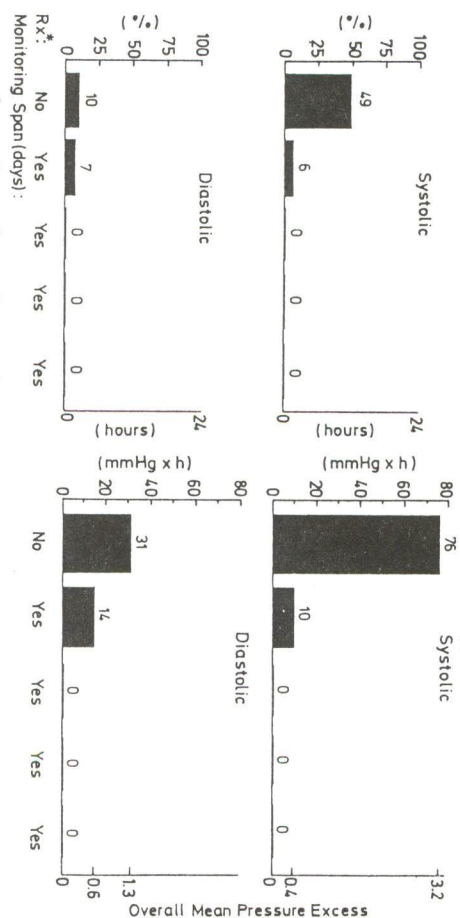
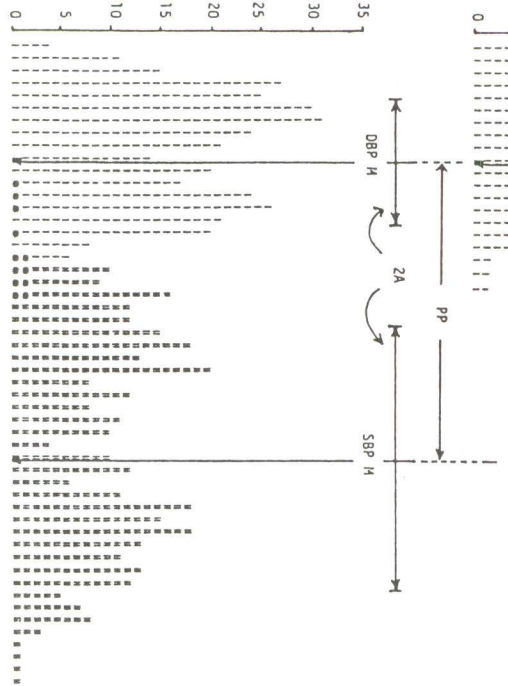


Fig. 8. Nonparametric blood pressure assessment. The question may be debated as to whether one should treat, by drugs, a systolic and a diastolic blood pressure (BP) of 128 and 82 mmHg, respectively. In this case, it was treated and the BPs were reduced by treatment at an appropriate time. Off treatment, the BPs were above peer-group limits 49% (SBP) or 10% (DBP) of the time, after treatment excess was eventually eliminated (left). The corresponding reduction and eventual disappearance of blood pressure excess, measured in mmHg $\times$ h, denoted as "hyperbaric index," is also shown (right). * Chlorothiazide 25 mg by mouth, mornings.

Calendar Month and Year: Dec 81-Jan 82 June 83 June 84 Dec 85-Jan 87

Number of values



tive) for comparison. The chronobiologic endpoint, the circadian amplitude, was invariably the most sensitive parameter for blood pressure. For heart rate, the MESOR appears superior. A circadian population rhythm characterizes systolic blood pressure ($P = 0.009$), mean arterial pressure ($P = 0.014$) and diastolic blood pressure ($P = 0.011$) of the newborns with a positive family history of high blood pressure but not of those with a negative family history ($P > 0.2$). For heart rate, a population rhythm is apparent in both risk groups. Individually, the rhythm is demonstrable in only about 35% of the newborns.

The effect of covariates such as sex, body mass index ($BMI = \text{weight}/\text{height}^2$) at birth and age at start of monitoring was further examined. Linear regression of these variables as well as maternal and gestational age on dynamic indices of blood pressure and heart rate variability was also performed.

Dispersion indices of heart rate increase as a function of the newborn's age at start of monitoring ($P < 0.05$); there is little if any effect of BMI on heart rate; newborns in the positive family-history group have a lower heart rate MESOR than those in the negative family-history group; girls have a larger heart rate MESOR as compared to boys ($P < 0.05$). A gender effect is not seen for blood pressure. Location and dispersion indices for newborns with a positive family history are larger than those of newborns with a negative family history, and contrary to expectation from studies in older children, location and dispersion indices are smaller in babies with a larger BMI ($P < 0.05$).

AUSTRALIAN THERAPEUTIC TRIAL IN MILD HYPERTENSION CONTROL GROUP: N=1943

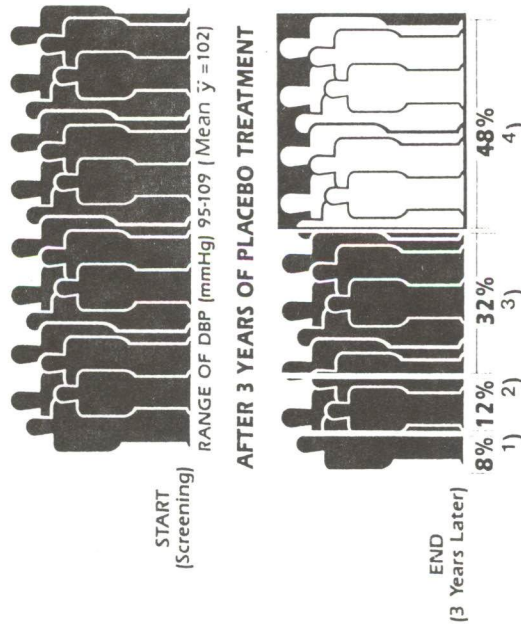


Fig. 5. ¹⁾ Ischemic coronary heart disease or stroke; ²⁾ > 109 DBP (mm Hg); ³⁾ 95–109 DBP (mm Hg); ⁴⁾ < 95 DBP (mm Hg) $\bar{y} = 91$.

The large proportion in clinical trials of “placebo responders” may be explained in part by entering individuals with “white coat” hypertension, i.e., by false positive diagnoses, relying on one or a few casual blood-pressure measurements. In a multi (60) million dollar clinical trial, 48% “cures” from placebo may be: in part placebo responders; in part false responders to start with, and; in part false negatives at the end

False-negative Diagnoses

In Fig. 7, a patient’s systolic blood pressures (SBPs), shown as dots, are mostly within the reference interval of peers during midday (when he is usually examined by his physician). At other times, however, notably at night, many of his SBPs are above the upper chronobiologic reference limit. The treatment of this patient was assumed to be satisfactory on a casual midday measurement basis. It is not, however, adequate in a chronobiologic perspective. Fig. 7 shows why the same misdiagnosis applies to the same patient’s diastolic blood pressures.

Therapy

Both the timing of treatment and the assessment of treatment effects are a chronobiologic matter. Figure 8 exemplifies a successful treatment insofar as it is judged by the reduction to zero of both the circadian percent time elevation of blood pressure and the circadian hyperbaric index. The upper graph in Fig. 8 (circadian percent-time elevation) shows that when the patient was off treatment, even though his means were below conventional limits, he was actually above a chronobiologic limit 49% of the time for systolic and 10% for diastolic blood pressure. This percentage time was reduced by treatment to small, negligible values and to zero thereafter.

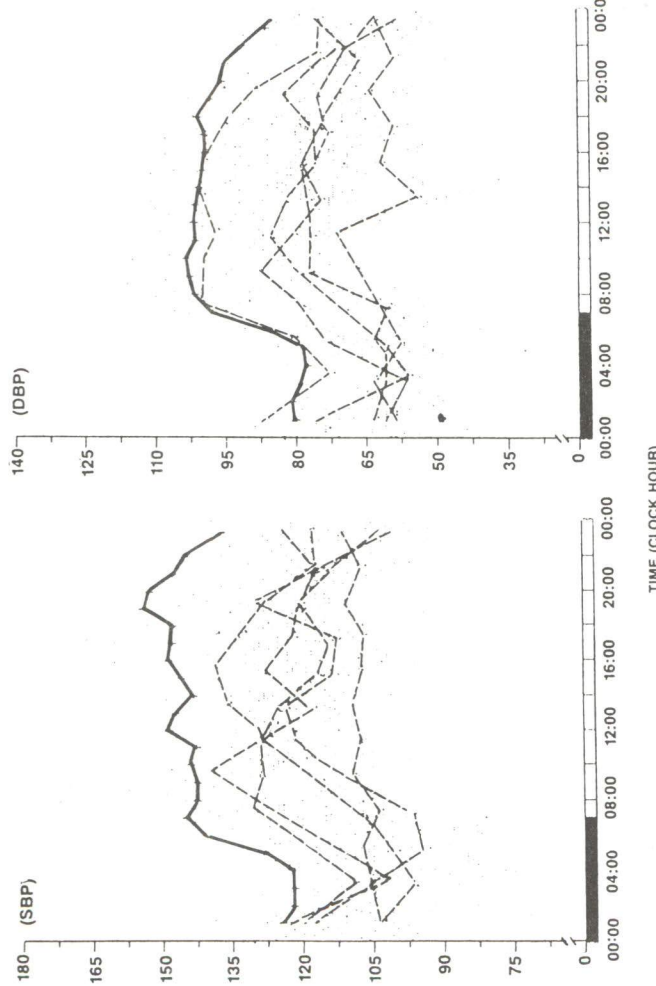


Fig. 6. False-positive diagnosis. The figure shows single measurements (as dots) of ambulatory systolic (S) blood pressure (BP) (left) and of diastolic (D) BP (right) from five subjects who, on three different office visits, had a standing DBP higher than 95 mm Hg and were labeled “borderline hypertensive”. Hourly mean values (dashed lines) drawn for each subject reveal that these individuals’ BP are mostly below the solid line representing the upper time-varying 95% prediction limit computed from the data of 39 clinically healthy individuals, used as a peer group reference range. In the absence of around-the-clock monitoring, such individuals could have been (mis)treated for long spans, perhaps for a lifetime. In these cases, failure to comply with treatment is desirable for the person involved. It should be noted that some individual values are around 170 mm Hg, whereas others are around 90 mm Hg. Note different vertical scales

In this case, then, a snapshot in mm Hg was replaced by the estimate of an index of excess expressed in mm Hg $\times$ h. Future work will have to provide for respite and a nonlinear accumulation of harm without thresholds by postulating the existence of an increasing harm function of blood pressure. Such a harm function should estimate the pressure-related cardiovascular disease risk by a pressure-related health index (PRHI), time-qualified as discussed elsewhere [13, 25]. The step from mm Hg to mm Hg $\times$ h, from the use of a fixed to that of variable threshold, and the use of parameter tests to assess the statistical significance of a change in indices may represent a step toward reducing harm associated with diseases related to a high blood pressure [12, 17].

Prevention

Chronobiology emphasizes prevention and seeks the tools to recognize risk as early as birth. Sensitive indices of blood pressure dynamics can actually be used to probe

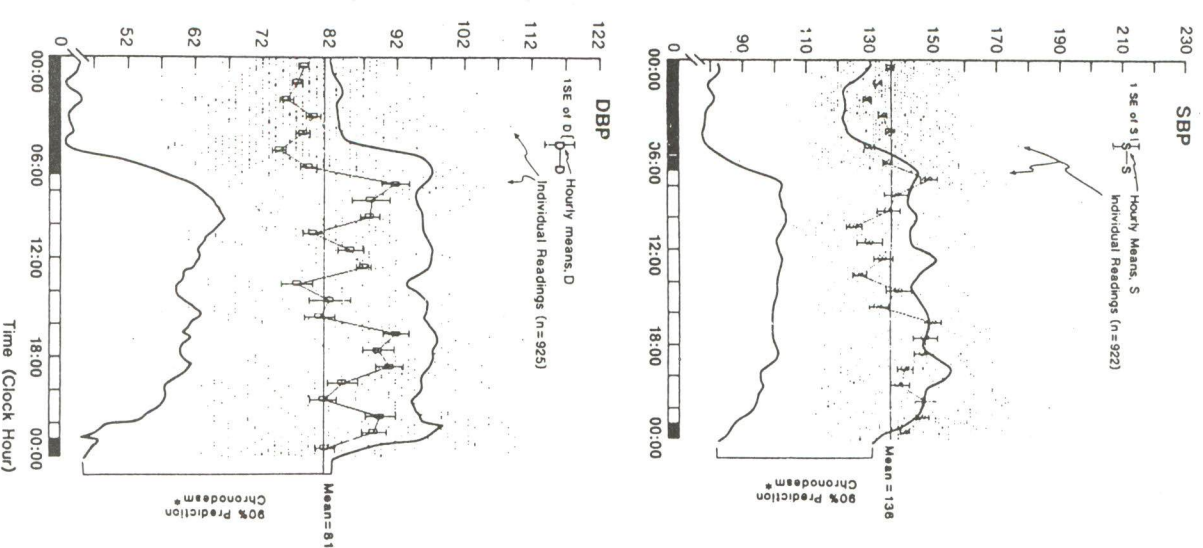


Fig. 7. High blood pressures (*BP*) at odd times contrast with mostly acceptable *BPs* around noon in a patient believed to be well-treated on the basis of a casual examination at midday. Systolic *BPs* shown on top (*SBP*); diastolic *BPs* on the bottom (*DBP*). Based on data at 7.5 min intervals for 24 h from 39 clinically healthy men, 23–59 years of age. Note different scales

compared with upper and lower limits of a standard profile done for a large peer group [20]. If the individual plot strays outside of the limits of the peer group at a given point in 24 h, this may be termed an excess as defined for that person with respect to the peer group. If, for example, the patient's plot is above the upper limit of the peer group for, say, 2 h by 10 mmHg, then the area between the curve and the limit represents the pressure $\times$ time excess. To get the area accurately, it has to be integrated by computer. Therefore, even if the person is normotensive for 22 h of the day, there will be a $2\text{-h} \times 10\text{ mmHg}$ excess day after day. Over time, this excess could explain possible increases in morbidity and mortality. Repplotting this curve after taking corrective action (e.g., drugs, sodium restriction or addition, etc.) will adequately show the results of the therapy, as compared to sole reliance upon measurements at office visits.

Based on the studies done using the chronobiologic approach to blood pressure recording and analysis, it has become clear that many people are being treated for high blood pressure who need not be [25] and that there are probably many others who should receive treatment but whose blood pressure elevation has not been detected.

False-positive Diagnoses

That the traditional approach is unsatisfactory can be suggested on the basis of a scholarly analysis of data published by Wilcox, Mitchell and Hampton [46]. These authors raise the suggestion whether clinical practice should be based on the results of clinical trials. On the basis of the results from these same clinical trials, Pötschke-Langer and Apfelbach instead advocate the use of a "smörgåsbord" of drugs [33]. The chronobiologically unacceptable design of the reviewed studies may be considered.

The outcome of large-scale clinical trials such as the Australian Therapeutic Trial in Mild Hypertension reflects the situation best. As shown in Fig. 5, out of nearly 2000 individuals in this study who received a placebo, almost half responded to this treatment, most of them within less than a year [25]. A high percentage of responders to placebo renders it likely that "office hypertension" leads to the entry into large-scale studies of many false positive cases. This point is also apparent from Fig. 6.

By the same token, the exact numbers of those treated with placebo and "converting" from "hypertension" to "normotension" must not be taken seriously. A substantial error in diagnosis may well be made in clinical trials and otherwise, not only at the outset of a study in terms of many false positives entering the study, but also at the final evaluation in which the ratio of "cured normotensives" is likely to be complicated by a substantial number of false-negative diagnoses. The outcome is somewhat less ambiguous in those studies relying on endpoints such as mortality and incidence of heart attack, stroke, etc., that are directly related to actual cardiovascular disease, irrespective of any blood pressure measurement; but in these cases as well, the uncertainty associated with the diagnosis at the entry into the study may greatly complicate or even invalidate the outcome.

CAREGIVING MERGED WITH CHRONOBIOLOGIC OUTCOME ASSESSMENT, RESEARCH, AND EDUCATION IN HEALTH MAINTENANCE ORGANIZATIONS*

Franz Halberg, Germaine Cornélissen, and Earl Bakken

University of Minnesota (F.H., G.C.) and Medtronic Inc. (E.B.),
Minneapolis, MN, USA

'Each of us can do more for our own health than any doctor, any hospital, any machine, or any drug' (Califano, 1986; cf. also Halberg, 1970, and Halberg et al., 1973).

'Reading, 'riting, 'rithmetic—and rhythms: a new "relevant" "R" in the educative process' (title of a paper by Halberg F., Halberg J., Halberg Francine, Halberg E. in *Perspect. Biol. Med.* 17: 128-141, 1973).

INTRODUCTION

When health care costs are staggering, solutions are needed at all levels, local, national and international. Attempts at cost containment need not consist solely of an across-the-board rationing of care and suggestions toward the creation of a national health care system. The quantity of needed care may be maintained while its quality is actually raised if the cost-effectiveness of care would be improved by the switch in emphasis from the proverbial pounds of cure to the ounces of prevention and education, advocated by a novel field of science, chronobiology. Humane, medical, technological and scientific viewpoints all dictate the blending of quality control and

*Acknowledgement. This version reflects comments by many who have had an interest in the quality of health care in an era of indispensable concerns about equity and cost containment. Disease prevention with chronobiologic computer literacy and self-help acquired in the context of the family and/or earliest education might achieve all three goals as advocated, in particular in a lifetime's cooperation and friendship with Lawrence E. Scheving, to whom these Proceedings as a whole are being dedicated. Special thanks are due to Cherie Perlmutter, Acting Vice-President for Health Sciences at the University of Minnesota, in whose title 'acting' reflects cogent and concerned action. Recommendations made herein apply broadly beyond HMOs.

systematic outcome assessment in care delivery, with chronobiologic concepts, facts and methods. The latter apply to various medical specialties. Chronobiologic outcome research and education in the context of care provided within a health maintenance organization (HMO) could become a potential hub of international lifespan studies for the collection of reference values as a step toward the chronobiologic optimization of health care and cure.

Table 1

TWO VIEWS OF MEDICINE AND BIOLOGY

VIEW	HOMEOSTATIC	CHRONOBIOLOGIC
1. REALITY	SET POINTS	RHYTHMS
2. ENDPOINTS	MEAN $\pm$ SE	MESOR PERIOD(S) AMPLITUDE(S) ACROPHASE(S) (WAVEFORM)
3. PHYSIOLOGIC RANGE OF VARIATION	BROAD RANDOM	NARROW SPECTRALLY STRUCTURED PREDICTABLE
4. SOURCES OF VARIATION	EXOGENOUS: RESPONSE TO EXTERNAL STIMULI	ENDOGENOUS AND EXOGENOUS: GENETIC PROGRAM, INCLUDING SPECTRAL STRUCTURE, ALLOWING FOR ANTICIPATION OF STIMULI, PREPARATION FOR THEM, AND PREVENTION OF HARM
5. HIERARCHY	UP/DOWN	COLLATERAL AND UP/DOWN
6. TELEONOMY	TIME-UNSPECIFIED RIGHTING REGULATION	LEAD-TIMED AND TIME-SPECIFIED PREPARATION AND CORRECTION COORDINATION
7. MECHANISM	FEEDBACKS (ERRATIC MODULATION) BETWEEN PAIRED ENTITIES ALONG AXES OF NETWORKS	FEEDSIDEWARDS (PREDICTABLE CHRONOMODULATION) AMONG MORE THAN TWO CONCOMITANTLY INTERACTING ENTITIES IN NETWORKS
8. SIMPLIFIED ANALOGY	THERMOSTAT	PENDULUM
9. BIOLOGIC IMPLICATIONS	DARWINISM (BASED ON NATURAL SELECTION OF RANDOM MUTATIONS THAT ARE EXTERNALLY ADAPTIVE)	INTERNALLY INTEGRATIVE AS WELL AS EXTERNALLY ADAPTIVE EVOLUTION
10. MEDICAL APPLICATIONS	MAINLY LIMITED TO DIAGNOSIS OF OVERT DISEASE BY VALUES OUTSIDE THE PHYSIOLOGIC RANGE TIME-UNSPECIFIED TREATMENT*	DIAGNOSIS AND TREATMENT REFINED BY NARROWED REFERENCE RANGE AND ASSESSMENT WITHIN THAT RANGE OF CHRONORISK LEADING TO PREVENTION
11. VALUE	WASTEFUL	COST-EFFECTIVE
12. PERSONAL SATISFACTION	FRUSTRATING WORK	SHEER FUN

*Notable exceptions such as vaccinations notwithstanding.

I. BACKGROUND

Chronobiology* is the study of mechanisms and applications of a structure in time characterizing all living organisms (Halberg F., 1969, 1970, 1977, 1983, 1987a-c; Halberg et al., 1977; Pauly, 1983; Reinberg and Smolensky, 1983; Scheving, 1976). As such, this computer-aided discipline applies to all of biology and medicine. It adds to the existing body of knowledge a key element, time, and does so even without the addition of any new experimental procedures.

Time, not only an additional variable, but a view of life. According to homeostasis (Guyton, 1986), it is important to clarify a putative regulation for constancy first, leaving rhythms as second-order phenomena. According to chronobiology, the recognition at the outset of the rhythmic structure in biology leads to an accurate and complete description of functional dynamics. Some basic physiology that otherwise remains unresolved, can be recognized only by applying the methods and concepts of chronobiology (Table 1). The putative homeostatic reality is based on set points. Chronobiologic reality consists of a multifrequency spectrum of rhythms. An up-down hierarchy of homeostasis is complemented in chronobiologic webs by a collateral hierarchy that recognizes and resolves a spectral structure within the physiologic range. Chronobiology hence renders predictable and exploits what otherwise is considered as exclusively random variation.

The rhythmic structure of living organisms is partly endogenous, genetically programmed, and thus differentially and rhythmically responsive to environmental cycles. In other words, variability is not only the consequence of responses to external stimuli, but is a feature of anticipatory behavior (Halberg, 1953). Feedback mechanisms striving toward regulation for a putative relative constancy (such as in a thermostat) are replaced by intrinsically periodic mechanisms (as illustrated by a pendulum) internally coordinated by feedsideward mechanisms (Halberg, 1983). Implications from the two views, notably for preventive health care, differ drastically. From the medical viewpoint, a deviation from the physiologic range serves mainly to diagnose overt disease. Chronobiologic considerations, in turn, aim at chronorisk assessment by values that may lie well within the physiologic range as a step toward prevention (Halberg, 1983). Cases in point are the elevation in extent of circadian blood pressure change during an uneventful pregnancy (Cornélissen et al., 1989; Kopher

*The science (logos) of time (chronos) and life (bios).

et al., 1989a and b) and in newborns (Halberg et al., 1986a, 1988b) as a function of the familial risk of high blood pressure.

Timing can be low-cost if not cost-free. Timing can be manipulated in much the same way as dosing. Chronobiology offers new concepts that can be applied for making recommendations as to when to sample and when to treat. Some of these concepts can be incorporated into today's clinical practice without the need to make major adjustments to the actual clinical procedures in use such as the timed use of corticosteroid, oncostatics, cyclosporine or antihypertensives and a long list of other drugs (Halberg, 1977; Halberg F. and Halberg E., 1984; Reinberg and Smolensky, 1983; Scheving, 1976). Chronobiology also offers new computerized tools for analyzing the data and for resolving a spectrum of rhythms, thereby adding new sensitive endpoints of dynamic characteristics of change as tools for timing treatment and for recognizing risk, thereby prompting preventive action (Halberg, 1969, 1983; Pauly, 1983; Reinberg and Smolensky, 1983; Scheving, 1976). The taking into account of rhythms, Tables 2-4 and Figure 1, can refine diagnosis and therapy.

High Technology. Timing can also be built into new devices for drug delivery (Halberg, 1987a) that already have applicability in diabetology and oncology (Halberg, 1982, 1987c). It seems likely that a much larger number of drugs may be optimized by timing their administration in the clinic, as has already been achieved in research (Cavallini et al., in press; Halberg F. and Halberg E., 1984).

TABLE 2
CHRONOBIOLOGIC CONCEPTS IN
CLINICAL PROCEDURE

C L I N I C A L D E C I S I O N	• Patient	Collection of risk information by filling out questionnaires inquiring about personal, familial and environmental history in relation to multiple disease conditions; standardization of pretest routine
	• Specimen	Timing of collection, as item in research, later as recommendation of sampling time
	• Sample	Time-specified single sample; serial monitoring of marker rhythms
	• Analytical procedure	Including chronobiologic methods of analysis
	• Result(s)	Time-qualified, with rhythm assessment on all serially monitored variables
	• Interpretation	By refined time-specified reference limits (personalized and/or derived from risk-qualified, gender- and age-matched healthy peers)

Software implementing chronobiologic concepts is particularly effective when it complements modern miniaturized and hence ambulatory recorders (e.g., of blood pressure, ECG, EEG, gastric acidity, core temperature, motor activity, etc.) and/or prostheses (pacemakers, cardioverter-defibrillators, drug pumps) (Bourgeois

TABLE 3

CHRONOBIOLOGIC MERGING OF OUTCOME RESEARCH AND PRACTICE

Allergy/Dermatology	Circadian time-specified skin tests Peak flow rhythms gauge severity of asthma and timed treatment (Rx, e.g., corticoid) effect
Eye	Intraocular pressure rhythms
Family practice	Physiologic monitoring by self-measurement and automatically, with chronobiologic analyses for purposes listed under other specialties
Internal medicine:	
• Cancer	Timing of drug and radiation Rx; programmed pumps
• Cardiology	Sudden death prediction; chronobiologic pacemaker-cardioverter-defibrillator
• Endocrinology	Hypercortisolism; multiple disease risk assessment; steroid timing
Mental health	Neuroendocrine approach to personality, with special reference to DHEA-S and drug addiction, anxiety, depression
Ob/Gyn	Assessment of eclampsia risk and of postnatal responsiveness to preventive low-dose aspirin treatment
Pediatrics	Blood pressure monitoring for cardiovascular disease risk assessment, neonatally and during adolescence; special focus on potential late effects of exposure to B-mimetics in utero
Quality assurance	Reduction of false positive as well as false negative diagnoses, e.g., of high blood pressure and associated side-effects and of cost of unnecessary Rx as well as of failures to treat when Rx is needed, respectively; optimization of all Rx by timing
Surgery	Home monitoring before and after surgery, e.g., for detection of nosocomial infection; timing of cyclosporine to reduce dose and side effects
Urology	Risk assessment in prostatic cancer; timing Rx in kidney cancer

et al., 1989; Halberg F. and Halberg E., 1984).

General applicability. The chronobiologists' interest in health care and cure (Callahan, 1987) is broad in two ways, both particularly germane to those grouped in organizations aiming primarily at health maintenance. One aspect is the study of the time structure of physiological variables in health and disease, which leads to the

TABLE 4

ROLE OF CHRONOBIOLOGY IN CLINICAL PRACTICE

Screening

- By accumulating and updating data base in health for deriving chronobiologically qualified reference values (chronodesms)
- By recognizing early alteration prompting closer monitoring and early intervention when needed

Diagnosis

- By determining when and how often to sample to reduce false positive and false negative diagnoses
- By adding rhythm characteristics as novel endpoints

Prognosis

- By providing means to assess changes on an individual rather than solely on a group basis

Therapy

- By timing drug or non-drug treatment
- By complementing chronopharmacokinetics with chronopharmacodynamics

Risk Assessment

- By assessing the spectral structure of endogenous and environmental rhythms
- By relating rhythm (or other) alteration to personal, familial and environmental history in relation to multiple disease conditions
- By uncovering new physiologic rules within the "physiologic range"

Prevention

- By timely and timed intervention based on early risk assessment

establishment of time-varying limits in lieu of fixed 'normal values' (Halberg and Montalbetti, 1983). Another aspect of chronobiology beyond timing is timely intervention.

Time-varying reference values, chronodesms. Presently, focus on an international scale, mostly on time-varying 90% prediction limits for blood pressure and heart rate, is intense (Carandente F. et al., 1989; Cornélissen 1987; Cornélissen et al., 1988, 1989; Cugini et al., 1987; Ferrazzani et al., 1989; Halberg, 1983; Halberg et al., 1988a and b, 1989a and b; Halberg J. et al., 1987, 1989; Hermida et al., 1986; Mainardi et al., 1988; Otsuka et al., 1989; Scarpelli et al., 1988; Schuh et al., 1989; Tamura et al., 1989; Tarquini et al., 1979, 1988). Yet other variables from gastric acidity over core or breast temperature, to any laboratory determination, also vary with time. This variation

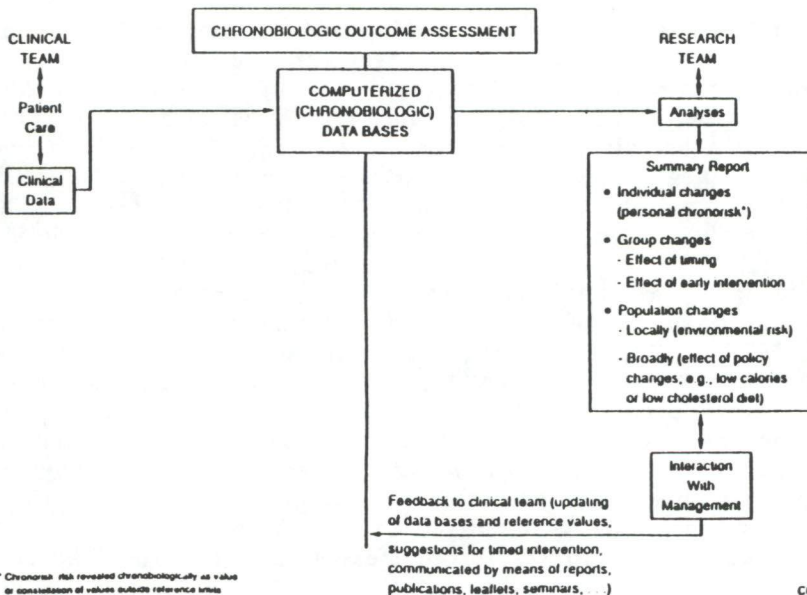


Figure 1: Chronobiologic outcome assessment, a dividend from HMO computers receiving reliably coded temporal information. © Franz Halberg.

should be medically exploited whenever possible (Halberg and Montalbetti, 1983; Haus et al., 1988). A recent step in this direction has been made by the detection of rhythms in routine quality control data in clinical chemistry in variables such as serum cholesterol, triglycerides, total bilirubin and serum iron (Borghi et al., 1989). Circadian, circaseptan and circannual rhythms all characterize circulating cholesterol; most recently, we have also detected rhythms in high- and low-density lipoproteins—HDL, LDL and VLDL (Singh et al., 1989).

The next step will be to exploit such information in the form of time-specified ranges of acceptable values, the chronodesms (Halberg et al., 1982b, 1988b). By accumulating data and organizing them into proper data bases, reference standards can be derived both for the acceptability of a single value of a variable such as blood pressure specified as a function of sampling time, and for the rhythm characteristics derived from serial measurements.

Marker rhythms: rhythm alteration before fever

Rhythms can be of use in monitoring and decision making. The availability of reference data can serve for determining optimal modalities, not only for timing treatment but also for recognizing early rhythm alteration preceding the further developments toward an overt disease condition. This feature, uniquely offered by chronobiology, should be very attractive to physicians in HMOs, even if chronobiology is pertinent to the 'solo' care provider as well. Timely chronobiologic screening makes it possible to recognize risk, before disease sets in. Breast temperature monitoring by manual recorders has served for detection of an elevation of the risk of developing breast cancer (E. Halberg et al., 1978, 1979, 1981a). Breast-specific temperature (corrected for the systematic differences of oral temperature from its mean during the menstrual cycle) was also measured by automated non-invasive instrumentation called the 'Chronobra' for 16 progesterone cycles in women at normal risk for breast cancer and for 15 cycles in women at high risk for breast cancer (defined as the breast ipse- or contralateral to a locally excised, histologically proven carcinoma). The rhythm-adjusted mean (MESOR) of the high-risk cases was warmer than in the controls (35.1 vs. 34.6°C; $P < .02$). The menstrual cycle-related temperature rhythm, present in the controls, was not detected in the high-risk cases. Instead, a circaseptan rhythm (with a period of about 7 days) was found in some, but not all, high-risk cases and characterizes the high-risk population as a whole. This component is not detected in the controls. The difference in circaseptan amplitude between the two

groups is statistically significant (0.03 vs. 0.24°C; $P < 0.05$) (Simpson et al., in press).

An earlier linear discrimination analysis by multiple regression of the breast temperature time series from 16 healthy breasts and 12 high-risk breasts showed the possibility of separating these two populations completely (100% discrimination). This is achieved when data from 16 of the 21 monitoring days are entered as predictors (Simpson et al., 1989).

Another promising chronobiologic application relates to surgery. Automatic rectal temperature monitoring has detected a circadian rhythm alteration prior to fever associated with a severe nosocomial infection. Almost certainly, this condition could have been prevented if antibiotic treatment had been initiated at the time of the (retrospectively detected) rhythm alteration immediately following ambulatory surgery (Halberg E. et al., 1981a).

In addition to focus on blood pressure, cholesterol, other cardiovascular variables and temperature, serial peak flow self-measurements, notably in the elderly, may serve for multiple aims: to exercise the lung in health, as can be seen from a gradual statistically significant improvement of performance (E. Halberg et al., 1981b); to detect any effects of pollution (Stupfel et al., 1977), or to monitor treatment in asthmatics (Halberg, 1987b).

II. WORK WITH GROUP HEALTH INC. (GHI)

On a group basis, risk recognition in the case of a positive personal and/or family history of high blood pressure and cardiovascular disease has become possible through our ongoing work at GHI and elsewhere (Schuh et al., 1989). Work has focused on pregnant women (Cornélissen et al., 1987, 1989; Kopher et al., 1989a and b), extending the scope of work on pregnant women by others (Carandente F. et al., 1989). An ambulatory monitor from Colin Medical Instruments (12677 Silicon Dr., San Antonio, TX 78249; Figure 2 bottom right) was used. Results from the GHI study summarizing data provided by 66 pregnant women contributing 92 profiles at hourly intervals for about 48 hours reveal an overall range of change as large as 58 and 40 mm Hg for systolic and diastolic blood pressure, respectively, and 47 beats per minute for heart rate. During pregnancy, the circadian rhythm-adjusted mean or midline-estimating statistic of rhythm (MESOR) of heart rate increases steadily as a function of gestational age, whereas that of blood pressure decreases to reach a minimum around the 20th gestational week before starting to increase again until

Table 5
Changes in the course of pregnancy of MESOR and circadian amplitude of blood pressure and heart rate

Variable*	1st trimester (n=19)		2nd trimester (n=46)		3rd trimester (n=24)		1-way ANOVA	
	Mean ± SE		Mean ± SE		Mean ± SE		F	P
<u>MESOR</u>								
SBP	109.8 ±	2.6	108.8 ±	1.4	115.0 ±	2.6	2.647	0.077
MAP	82.5 ±	2.0	81.7 ±	1.2	87.5 ±	1.9	3.744	0.028
DBP	63.5 ±	1.6	63.3 ±	0.9	68.3 ±	1.6	4.653	0.012
HR	80.1 ±	1.9	82.1 ±	0.9	86.9 ±	1.9	4.704	0.012
<u>Circadian amplitude</u>								
SBP	10.87 ±	0.81	11.51 ±	0.61	9.36 ±	0.92	2.150	0.123
MAP	10.12 ±	0.84	10.06 ±	0.62	9.13 ±	1.12	0.398	0.673
DBP	7.52 ±	0.66	7.76 ±	0.45	7.36 ±	0.72	0.131	0.877
HR	8.62 ±	0.95	9.87 ±	0.54	8.66 ±	0.84	1.105	0.336

*SBP=systolic blood pressure; MAP=mean arterial pressure; DBP=diastolic blood pressure; HR=heart rate. Mean and standard error (SE) expressed in mm Hg (SBP, MAP, DBP) or bpm (HR).

Table 6
Changes with gestational age in blood pressure (BP) and heart rate (HR)*

Gestational age (weeks)	n	Systolic BP		Diastolic BP		HR	
		$\bar{y} \pm SE$	RV	$\bar{y} \pm SE$	RV	$\bar{y} \pm SE$	RV
12	8	-.450 ± .115	99.60	-.381 ± .127	99.43	+.245 ± .114	100.30
13	9	-.462 ± .102	99.20	-.367 ± .113	98.88	+.100 ± .177	100.42
14	9	-.462 ± .102	98.79	-.367 ± .113	98.33	+.100 ± .177	100.55
15	10	-.428 ± .098	98.41	-.329 ± .108	97.83	+.159 ± .169	100.74
16	14	-.240 ± .132	98.20	-.180 ± .119	97.56	+.104 ± .123	100.87
17	14	-.240 ± .132	97.99	-.180 ± .119	97.29	+.104 ± .123	101.00
18	15	-.220 ± .125	97.80	-.158 ± .113	97.05	+.133 ± .118	101.16
19	14	-.210 ± .129	97.61	-.105 ± .106	96.90	+.124 ± .128	101.32
20	13	-.041 ± .140	97.58	+.035 ± .103	96.95	+.207 ± .086	101.57
21	13	+.082 ± .145	97.65	+.128 ± .103	97.14	+.149 ± .088	101.75
22	14	+.102 ± .135	97.74	+.146 ± .091	97.36	+.224 ± .092	102.03
23	14	+.206 ± .118	97.92	+.202 ± .085	97.66	+.249 ± .090	102.34
24	14	+.206 ± .118	98.10	+.202 ± .085	97.97	+.249 ± .090	102.64
25	15	+.114 ± .144	98.20	+.153 ± .092	98.20	+.336 ± .121	103.05
26	15	+.175 ± .149	98.36	+.188 ± .094	98.48	+.380 ± .126	103.52
27	13	+.261 ± .157	98.59	+.253 ± .092	98.86	+.397 ± .137	104.01
28	12	+.262 ± .171	98.82	+.250 ± .100	99.23	+.438 ± .142	104.55
29	10	+.220 ± .204	99.01	+.244 ± .120	99.60	+.492 ± .166	105.16
30	8	+.415 ± .161	99.37	+.351 ± .105	100.13	+.352 ± .146	105.59
31	7	+.519 ± .141	99.83	+.410 ± .101	100.74	+.328 ± .166	105.99
32	6	+.625 ± .110	100.38	+.477 ± .089	101.46	+.269 ± .183	106.32

*To show qualitative trends, notwithstanding dilution of results due to sparse sampling, twice or thrice during pregnancy. n is number of women providing 2 consecutive profiles bracketing this gestational age; $\bar{y} \pm SE$ is mean and standard error of rate of change expressed as mm Hg/week for systolic and diastolic BP and as bpm/week for HR; RV is relative value determined by computing the average MESOR of profiles obtained in the 12th gestational week (P-12) and reconstructing the changes in the course of pregnancy by adjusting this value weekly by the average weekly rate of change, then expressing the results as a percentage (equating P-12 to 100% to allow for inter-individual differences in BP and HR MESORs).

Table 7
Contribution of first 6 harmonics to waveform of circadian blood pressure (BP)
and heart rate (HR) during pregnancy*

Harmonic number (period in h)	Systolic BP			Diastolic BP			HR		
	% SS	$\bar{y} \pm SE$	Med	% SS	$\bar{y} \pm SE$	Med	% SS	$\bar{y} \pm SE$	Med
1 (24)	90.5	36.0 $\pm$ 1.8	35.5	84.9	33.5 $\pm$ 1.7	34.0	87.1	36.2 $\pm$ 1.9	36.0
2 (12)	34.5	8.5 $\pm$ 0.9	6.5	41.9	8.8 $\pm$ 0.9	6.5	30.6	7.2 $\pm$ 0.7	5.0
3 (8)	14.3	4.0 $\pm$ 0.5	3.0	10.5	4.8 $\pm$ 0.4	4.0	20.0	5.7 $\pm$ 0.6	5.0
4 (6)	13.1	3.6 $\pm$ 0.4	2.0	8.1	3.5 $\pm$ 0.5	2.0	12.9	3.9 $\pm$ 0.5	3.0
5 (4.8)	8.3	3.9 $\pm$ 0.4	3.0	7.0	3.7 $\pm$ 0.4	3.0	12.9	4.3 $\pm$ 0.5	2.0
6 (4)	2.4	2.6 $\pm$ 0.3	2.0	7.0	3.4 $\pm$ 0.4	2.0	10.6	3.0 $\pm$ 0.3	2.0
Overall model	85.7	58.7 $\pm$ 1.4	59.0	82.6	57.6 $\pm$ 1.3	58.5	81.2	60.4 $\pm$ 1.6	62.0

*The fit of multiple harmonics serves the attempt to account for any nonsinusoidal waveform expressing intrinsic circadian features, for any contribution by intrinsic ultradian components, and for the effects of a variety of extrinsic factors, such as meals or exercise.

Numbers of profiles used are 84, 86 and 85 for systolic and diastolic BP and HR, respectively; series with missing values over spans too long to fit this 6-component model omitted;

% SS=percentage of series for which a given component showed statistical significance ($P < 0.05$).

$\bar{y} \pm SE$ =mean and standard error of percentage rhythm (in %).

Med=median of percentage rhythm (in %).

Table 8
Circadian period of blood pressure and heart rate during pregnancy

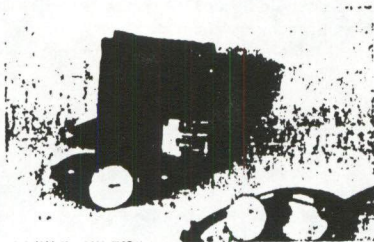
Variable/ Endpoint	One-component model			Two-component model					
	24-h component			24-h component			12-h component		
	n	Mean $\pm$ SE	Median	n	Mean $\pm$ SE	Median	n	Mean $\pm$ SE	Median
SBP									
Period	87	24.12 $\pm$ 2.61	23.94	82	24.92 $\pm$ 3.17	24.27	32	11.78 $\pm$ 1.78	11.90
Lower limit		22.04 $\pm$ 2.61	22.17		21.62 $\pm$ 3.43	22.10		10.83 $\pm$ 1.63	11.17
Upper limit		26.58 $\pm$ 3.35	25.52		28.23 $\pm$ 4.38	27.06		12.87 $\pm$ 2.04	12.94
MAP									
Period	82	24.38 $\pm$ 3.47	24.00	75	24.44 $\pm$ 2.12	24.09	32	12.37 $\pm$ 2.18	12.01
Lower limit		21.70 $\pm$ 2.94	22.13		21.65 $\pm$ 2.52	21.71		11.26 $\pm$ 1.60	11.17
Upper limit		27.46 $\pm$ 6.78	26.15		27.79 $\pm$ 3.88	27.04		13.44 $\pm$ 2.50	12.83
DBP									
Period	86	24.10 $\pm$ 2.73	24.05	73	24.55 $\pm$ 2.41	24.41	36	11.89 $\pm$ 1.44	11.73
Lower limit		21.71 $\pm$ 3.37	22.32		21.87 $\pm$ 2.95	22.20		10.78 $\pm$ 1.20	10.98
Upper limit		26.91 $\pm$ 3.78	26.36		27.71 $\pm$ 4.54	27.29		13.04 $\pm$ 1.78	12.74
HR									
Period	85	24.39 $\pm$ 2.56	23.97	82	23.86 $\pm$ 2.33	23.99	34	12.51 $\pm$ 1.83	12.33
Lower limit		22.26 $\pm$ 2.05	22.25		21.63 $\pm$ 2.47	22.01		11.47 $\pm$ 1.58	11.56
Upper limit		27.12 $\pm$ 4.98	25.96		26.40 $\pm$ 3.51	26.45		13.75 $\pm$ 2.50	13.31

SBP=systolic blood pressure; MAP=mean arterial pressure; DBP=diastolic blood pressure; HR=heart rate. Lower and upper limits refer to 95% confidence limits for the period; n number of series for which a 95% confidence interval could be determined for the period. Mean, standard error (SE) and median in hours.

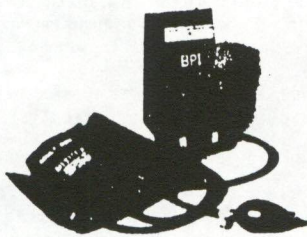
delivery (Tables 5 and 6) (Cornélissen et al., 1989; Kopher et al., 1989a and b). The MESOR and a measure of one-half of the predictable (since rhythmic) change, the circadian amplitude, of blood pressure are correlated with a cardiovascular risk index

New instrumentation for 48-hour or longer monitoring renders chronobiologic monitoring practical since many persons lack the discipline required for self-measurement, and since self-measurement is not possible under some ordinary conditions and/or during sleep. Chronobiology, however, requires more than the use of special instrumentation. Without chronobiologic analyses, much invaluable information is lost.

Instrumental developments are helpful, as compared to a traditional sphygmomanometer



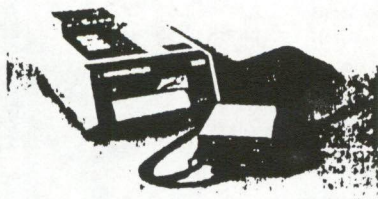
Used with a stethoscope,



a digital-reading instrument has the advantage of simplicity and does not depend upon hearing.



Instruments that record automatically once the measurement process is started or fully automatic room-restricted monitors represent further progress, notably since the former allow a good review of blood pressure during daytime activities, and the latter provide measurements during sleep as well.



Fully ambulatory, truly portable lightweight instrumentation is highly desirable, however, even if it is not indispensable. Automatic monitors are best combined with the use of manual instruments. Thus, after an automatic 48-hour or 1-week profile, checks required on a daily basis in patients with accelerated high blood pressure may be carried out manually, until the automatic instrumentation becomes priceworthy.

Figure 2: A few steps from the sphygmomanometer with a stethoscope toward (the as-yet utopia of) an implanted monitor of cardiovascular and other psychophysiological functions. © Franz Halberg.

developed on the basis of questionnaires inquiring about the personal and familial history of high blood pressure. This correlation is further improved by the consideration of higher-order harmonics considered to approximate more closely the circadian waveform, Table 7. Additional endpoints such as the circadian period (Table 8) are being considered to achieve further discrimination between low-risk and high-risk pregnancies.

Work at GHI has also extended the scope of earlier findings on newborns (Cornélissen et al., 1987; Halberg et al., 1986a, 1987a, 1988b). In cooperation with colleagues in Florence (Mainardi et al., 1988; Tarquini et al., 1988), cardiovascular functions were automatically monitored on 164 newborns at half-hour intervals for 48 hours during the first week of life. On the basis of an inspection of time plots of the data, the naked eye cannot readily discern any rhythmic pattern. With chronobiologic methods, however, a circadian rhythm in blood pressure and heart rate can be demonstrated below the .001 level of statistical significance, notwithstanding its relatively low circadian amplitude, Table 9. When the computer-resolved data are summarized along a 24-hour scale, the high values in these cardiovascular rhythms (the acrophases) occur around 0600, a timing nearly opposite that encountered in the newborns' mothers before and after delivery and also opposite that encountered in other adults, for whom blood pressure usually peaks in the afternoon. This finding suggests that, as a group phenomenon, not only the actual beat of the heart but also a circadian 'beat' of the heart rate are present at birth (Halberg et al., 1988b; Kellerová, 1981).

As group phenomena, neonatal cardiovascular rhythms are also demonstrated along the scale of a week and of a year. From the viewpoint of risk assessment, the circadian and the circaseptan rhythms appear to be more prominent in babies with a positive (N=94) than in babies with a negative (N=70) family history of high blood pressure, Tables 9 and 10. Whereas the circadian rhythm is at best of borderline statistical significance for babies with a negative family history, it is statistically significant for those with a positive family history. Thus, it appears that by the time of birth, the die is cast as to whether one is on a path toward high blood pressure later in life or toward an acceptable one. This finding, made on the basis of data collected in Florence, Italy, during 1985-1986, was also independently made in Rome on data obtained during the same span (Halberg et al., 1986a; DiPalma et al., 1987). The difference between newborns with a positive vs. negative family history of high blood pressure is obscured, however, in subsequent years in data from Florence, Italy, where the original observations were made. The circadian amplitudes of systolic, mean arterial and diastolic blood pressure increase with a P of 0.015, 0.046 and 0.008,

Table 9
Circadian rhythm in blood pressure and heart rate of
clinically healthy newborns*

Variable	Percent ** rhythm(%)	P	MESOR	Amplitude	Acrophase (360°=24h; 0°=00 ⁰⁰)
<u>All (n=164)</u>					
SBP	6	<0.001	71.8	0.94	-97°
MAP	6	0.001	58.3	0.76	-91°
DBP	7	<0.001	44.1	0.66	-90°
HR	4	<0.001	124.9	1.40	-26°
<u>NFH (n=70):</u>					
SBP	6	0.103	71.7	0.71	-91°
MAP	6	0.193	58.1	0.57	-65°
DBP	7	0.091	44.0	0.51	-83°
HR	4	0.012	126.2	1.04	-18°
<u>PFH (n=94):</u>					
SBP	6	<0.001	71.8	1.11	-100°
MAP	6	0.001	58.4	0.95	-102°
DBP	7	0.001	44.1	0.77	-94°
HR	4	<0.001	124.0	1.67	-29°

*Monitored automatically for ~48 h at ~30-min intervals during the first week of life, using an instrument manufactured by Colin Medical Instruments (San Antonio, TX).

**SBP=systolic blood pressure; MAP=mean arterial pressure; DBP=diastolic blood pressure; HR=heart rate. MESOR and amplitude expressed in mm Hg (SBP, MAP, DBP) or bpm (HR). NFH=newborns with a negative family history of high blood pressure and/or cardiovascular disease; PFH=newborns with a positive family history of high blood pressure and/or cardiovascular disease.

respectively, between 1985-86 and 1987-88. These secular changes are shown in Figure 3 and are of chronoepidemiologic interest in themselves. The change in the circadian amplitude of blood pressure in newborns may reflect some environmental, perhaps societal factor, or it may represent changes in health care, among other possibilities, deserving thorough scrutiny. Secular changes occur, of course, not only in putative indices of risk, but also in overt disease. Secular mortality variation among survivors of unstable angina and myocardial infarction is a case in point (Hickey et al., 1988).

To turn back to the possibility that intrauterine factors can change the circadian blood pressure amplitude, beta-mimetics to which a newborn had been exposed in the womb alter about-daily, about-weekly and about-yearly neonatal rhythms. Table 11 shows early

results (Halberg et al., 1988b and c). It is the more important, therefore, to note the overall consistency of the betamimetic effect upon the circadian blood pressure amplitude on a sample of 39 exposed newborns, as compared to 113 newborns not so exposed, Figure 4. Moreover, when the circaseptan and the circannual rhythm parameters of neonatal systolic and diastolic blood pressure were computed for idealized time series constructed separately for betamimetic-exposed and unexposed newborns at term, a betamimetic effect can be considered further for infradian parameters of the developing neonatal infradian system. By the betamimetic treatment of premature labor, the circadian, circaseptan and circannual blood pressure dynamics may all be changed: a newborn with a negative family history of high blood pressure and cardiovascular disease resembles one with a positive

Table 10
Comparison of circaseptan features between newborns with a negative or positive family history of high blood pressure¹

Variable Group (span in days)	PR	P	MESOR ± SE	Amplitude (95% CI)	Acrophase
1987 results based on 62 newborns§					
SBP (7)	NFH	18 <0.001	0 ± .34	2.04 (1.09, 3.00)	-37* (-10, -65)
-	PFH	64 <0.001	0 ± .32	5.53 (4.62, 6.45)	-176* (-166, -185)
DBP (7)	NFH	11 0.010	0 ± .26	1.17 (0.43, 1.91)	-124* (-85, -163)
-	PFH	63 <0.001	0 ± .23	3.79 (3.15, 4.43)	-176* (-167, -186)
SBP (7)	NFH (ed)	12 0.005	0 ± .34	1.60 (0.65, 2.55)	-47* (-10, -83)
-	PFH (ed)	55 <0.001	0 ± .40	5.72 (4.58, 6.86)	-174* (-162, -185)
DBP (7)	NFH (ed)	17 0.001	0 ± .26	1.49 (0.76, 2.23)	-138* (-109, -167)
-	PFH (ed)	60 <0.001	0 ± .25	3.95 (3.24, 4.66)	-180* (-169, -190)
SBP (6)	NFH	2 0.421	-0.09 ± .27	0.56 (. , .)	-148* (. , .)
-	PFH	60 <0.001	-0.82 ± .32	5.09 (4.10, 6.07)	-155* (-146, -164)
DBP (6)	NFH	39 <0.001	-0.35 ± .22	2.18 (1.52, 2.84)	-159* (-144, -174)
-	PFH	62 <0.001	-0.56 ± .21	3.48 (2.83, 4.13)	-155* (-146, -164)
SBP (6)	NFH (ed)	7 0.068	-0.16 ± .27	0.98 (. , .)	-159* (. , .)
-	PFH (ed)	48 <0.001	-0.83 ± .42	5.19 (3.89, 6.48)	-152* (-139, -164)
DBP (6)	NFH (ed)	51 <0.001	-0.43 ± .21	2.66 (2.03, 3.28)	-159* (-148, -171)
-	PFH (ed)	52 <0.001	-0.54 ± .25	3.36 (2.59, 4.14)	-157* (-145, -168)

¹SBP-systolic blood pressure; DBP-diastolic blood pressure; NFH-negative family history of high BP; PFH-positive FH; (ed): after eliminating data series from babies whose mothers had an elevated BP or were on medication during pregnancy. PR-percent rhythm (%); P-P-value from testing $H_0: A=0$; 95% CI = 95% confidence interval; MESOR and amplitude expressed in mm Hg; acrophase expressed in degrees, with 360°=168 h; 0°=time of birth. Parameter test results comparing NFH and PFH indicated by asterisks in the column of the parameter being tested: **P<0.01; *P<0.05; +.05<P<0.10.

§Analyses of residuals from first-order polynomial fit (linear trend); to reconstitute idealized time series from average differences between consecutive 2-h spans of individual series, starting value is mean of all data collected within the first 6 h of life.

Table 11

Beta-mimetic drug use (Rx) and perhaps corticoid use during pregnancy increases double circadian amplitude of blood pressure (BP) in newborns with a negative family history of high BP

Family history of high BP							
Negative				Positive			
Treated:							
No (n=20)*	Yes (n=8)	Δ	t (P)	No (n=26)	Yes (n=6)	Δ	t (P)
Systolic BP							
4.20	7.72	+3.52	3.124	6.22	5.68	-.54	0.630
$\pm .34$	$\pm .45$	± 1.12	(<.01)	$\pm .82$	± 4.24	$\pm .86$	(NS)
Mean arterial BP							
3.78	7.08	+3.30	3.531	5.82	5.26	-.56	0.874
$\pm .34$	± 3.48	$\pm .94$	(<.01)	$\pm .64$	± 3.16	$\pm .64$	(NS)
Diastolic BP							
2.98	6.36	+3.38	3.360	4.80	4.32	-.48	1.044
$\pm .32$	± 4.04	± 1.00	(<.01)	$\pm .60$	± 2.16	$\pm .46$	(NS)

*Family history of diabetes also negative.

such family history in the case of circadians, Figure 4. For the case of any betamimetic effect upon the circaseptan rhythms, the reverse also seems to be true (Wu et al., this volume).

The fact that a given intervention during pregnancy affects the time structure of cardiovascular functions of the newborn in an endpoint that reflects cardiovascular disease risk reflects just one side of a proverbial coin. It has an interesting implication for the other side of the same putative cardiovascular disease risk-related coin: it suggests the possibility that by proper intervention, short of manipulating genes, we may be able to help the baby at high risk and also that we may do so best by treating the mother during pregnancy.

Opportunities thus arise to test the timely administration of agents such as low-dose (100 mg/day) aspirin during pregnancy. These interventions aim at lowering perinatal morbidity and mortality, as already achieved in several studies in Europe (Beaufils et al., 1985; Wallenburg, 1988). We also aim, however, at possibly improving on the results by an individualized assessment of who should and who should not be treated for the lowering of the risk of eclampsia and related perinatal conditions (Ferrazzani et al., 1989). Chronobiologic results obtained so far indicate that such treatment may not be effective for all women. On an individualized basis, quite different results were obtained, with the qualification that the effect of regression to the mean was not controlled.

Moreover, these results can be interpreted in the light of the retrospectively-assessed outcome of pregnancy in terms of the presence or absence of pregnancy-induced hypertension.

Thus, statistically significant decreases in blood pressure were noted in 3 of 4 patients who eventually developed pregnancy-induced hypertension; of these, 1 was normotensive in profiles obtained just before and just after the week on aspirin. Statistically significant changes (1 decrease and 2 increases) in blood pressure were also seen in 3 of 15 patients who were not known to have developed pregnancy-induced hypertension (Ferrazzani et al., 1989). These results suffice to advocate tests of the merits of an

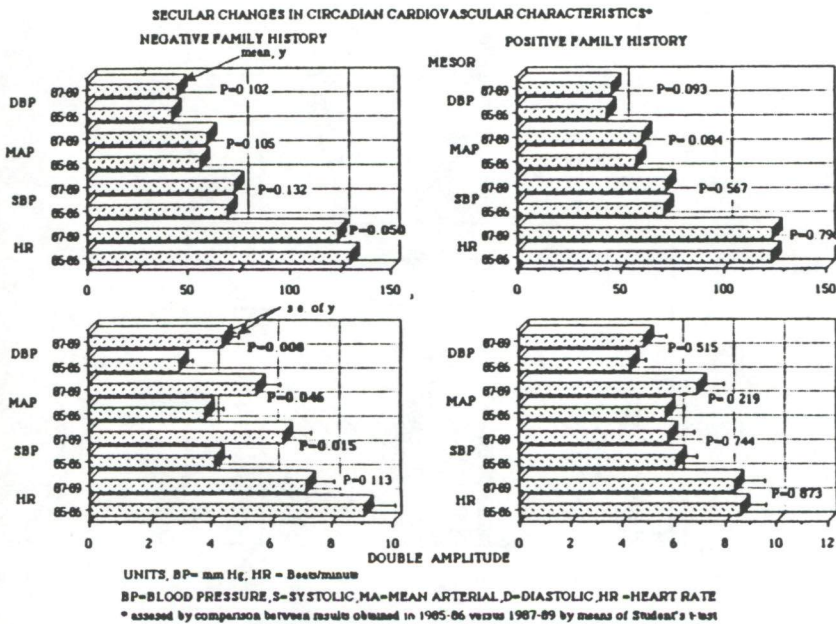
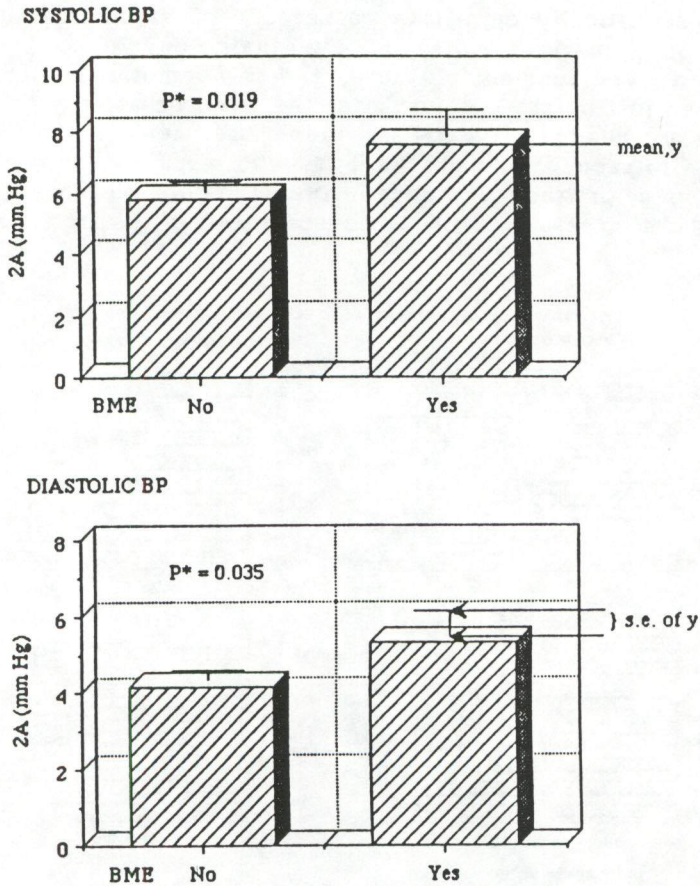


Figure 3: Statistically significant secular changes in circadian amplitude of blood pressure but not heart rate (bottom half) in the face of a change in heart rate but not blood pressure MESOR in newborns with a negative family history of high blood pressure.

Note importance of looking at more than a single rhythm parameter in more than a single risk group (and in both genders, as shown elsewhere in this volume by Fernández et al.).

Alterations in rhythm characteristics constitute sensitive gauges of changes in exogenous and/or endogenous factors. Analyses by Wu Jinyi; graph by José R. Fernandez Bernardez. For a drug effect in utero, see Figure 4.

EFFECT OF BETAMIMETIC EXPOSURE (BME) IN UTERO ON NEONATAL
CIRCADIAN BLOOD PRESSURE (BP) DOUBLE AMPLITUDE (2A)



N of newborns 113

39**

* P from Student's t-test

** Including 3 cases exposed to corticoid, one of them in addition to betamimetic.

Figure 4: Diethylstilbestrol revisited in the circulation?
Analyses by Wu Jinyi; graph by José R. Fernandez
Bernardez.

individualized assessment of the response to low-dose aspirin before long-term treatment is advocated during pregnancy or in the non-pregnant state. Indeed, one should aim toward possibly helping some (without treating many to no avail and at great cost, and even harming other) pregnant women with aspirin. This is, of course, a general principle, quite apart from drugs that may combine anti-hypertensive and anti-thrombotic effects.

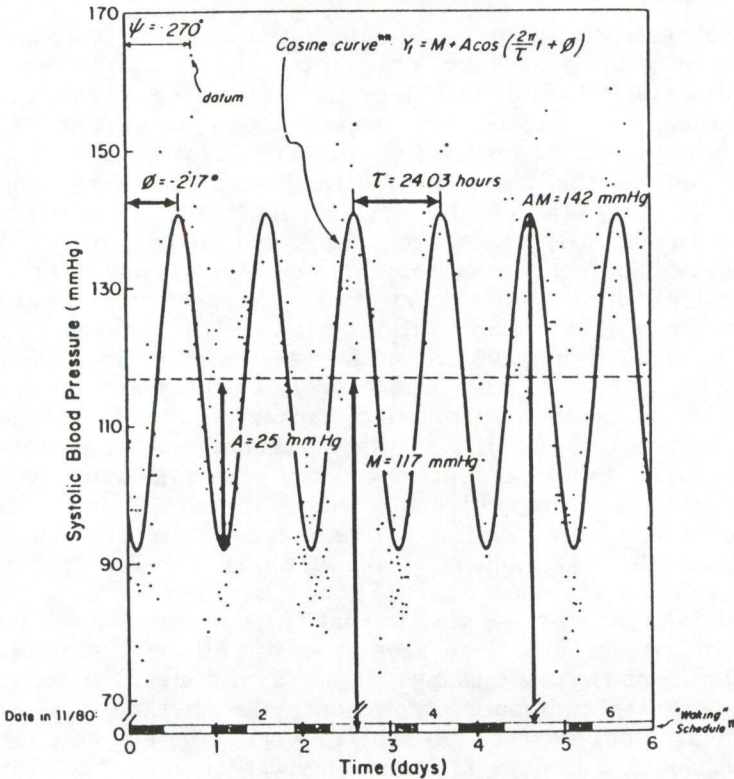
III. INTERNATIONAL LIFE SPAN STUDY

We are presently planning an international womb-to-tomb study. As noted above, work on pregnant women and newborns has already started and has led to interesting results. During pregnancy, the MESOR and the circadian amplitude of blood pressure correlate positively with a cardiovascular risk score developed on the basis of questionnaires inquiring about the personal and familial history of high blood pressure and cardiovascular disease. A broad rhythmic structure—the biologic day, week and year—are all expressed on a population basis at birth, but only the neonatal rhythm characteristics, and not conventional (statistical location) indices (such as means), help separate groups of newborns at low vs. high risk of developing a high blood pressure and/or cardiovascular disease later in life. During adolescence, only the circadian amplitude (not the MESOR) of blood pressure correlates with an echocardiographic index, the thickness of the interventricular septum, a measure of target organ involvement, corresponding perhaps to an increased cardiovascular disease risk, before there is target organ damage (Croppi et al., 1987; Halberg et al., 1988b; cf. also Halberg and Fink, 1981, for background). There is parsimony in using chronobiologic approaches to prevention: one may separate different risk groups at all ages by computing measures of extent and timing of rhythmic change, Figure 5, and mean values that are more accurate and more precise once the rhythms are assessed. The mean alone on occasion fails to work, whereas chronobiologic indices do so, e.g., 5 years after a myocardial infarction, when the chronobiologic approach, but not the conventional one, distinguishes the group of those who die from the group of survivors (Halberg et al., 1988b; Orth-Gomér et al., 1986), Figure 6.

Chronobiology from womb to tomb. Ongoing 'back burner' studies at GHI in the USA, in Germany, Italy, Spain and Japan, could be extended into a broader international endeavor by systematically sampling groups of individuals of both genders in different age

categories, e.g., 5 years apart, from birth, and eventually from conception, to death. These studies could greatly extend the scope of earlier nonchronobiologic longitudinal sampling with particular attention paid to physical and psychological growth, development and aging (Roche, 1980; cf. Falkner et al., 1980; Himes

Parameters of Circadian Rhythm
in Systolic Blood Pressure
Estimated by Non-Linear Least Squares Procedure*



* Applied to automatically recorded data from healthy woman 60 years of age

** Fitted to data by non-linear least squares, with Y_t = value of curve at time t ; M = mesor = average value of curve over integral number of cycles; A = amplitude = half of difference between highest and lowest value of curve; AM = acromeson = highest predicted value, T = period = duration of one complete cycle; ϕ = acrophase = timing of highest value in curve (here in relation to 00⁰⁰ on first day of data collection), with $360^\circ \pm T \psi$ = macrophase = timing of highest value. Procedure also provides confidence interval for parameters (M , A , T , and ϕ)

^{††} From automatic actometry; rest-span shaded

Figure 5: Rhythm characteristics: the chronobiologist's endpoints.
© Franz Halberg.

et al., 1981; Sontag et al., 1958). Some reports of these earlier nonchronobiologic endeavors recognize the need for the methods of chronobiometry. To cite Roche (1980) verbatim, 'effective curve fitting will:

- accurately summarize a large amount of data using a few parameters;
 - provide parameters that can be interpreted [chrono, insert ours] -biologically, and
 - smooth the data, thus removing random fluctuations. These fluctuations become 'residuals' and can be analyzed separately; ...'
- Indeed, the homeostatic investigators' noise or residuals become the chronobiometrist's parameters after proper analysis. Roche (1980) also notes that irregularities of tracking records apart from measurement error are due to variations in the timing of

Ventricular Ectopic Beats (VEBs) in Patients with Ischemic Heart Disease Who Survived (—) or Died (---) within 5 Years after a 24-Hour ECG Recording

Conventional (left) and Chronobiologic Approach (right) to the Prediction of Sudden Death

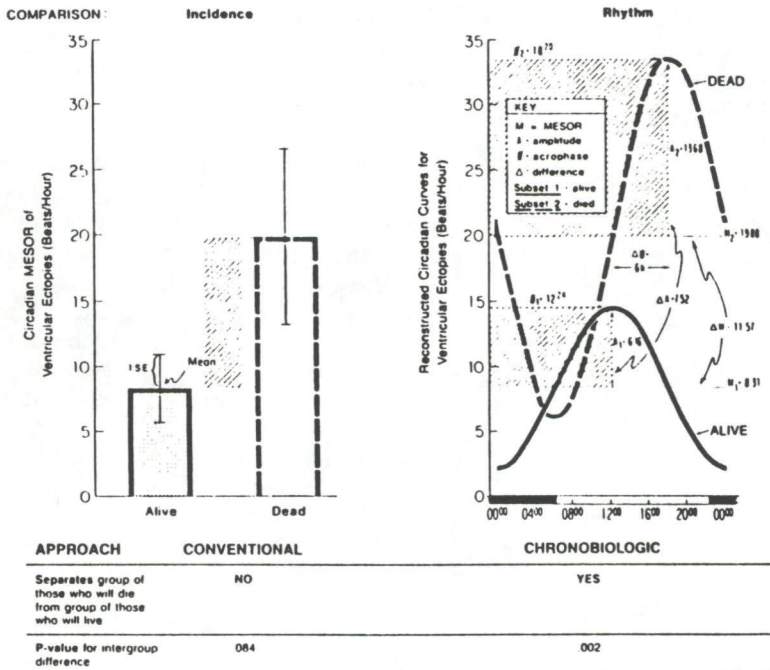


Figure 6: Chronobiometry of the ECG may work when the conventional 'Holter' approach fails. © Franz Halberg.

measurements, as well as to developmental and aging trends. Roche actually refers to the importance of the seasons, if not to that of the entire rhythm spectrum.

Circannual changes are indicators of an increased risk of developing a number of civilization diseases. Moreover, once reference standards are available, they can be sampled cost-effectively (Halberg, 1983; Hermida et al., 1985, 1986). For these reasons, chronobiologic reference standards should be gathered in health under specified conditions of personal and familial risk of developing a given disease investigated. The actual risk of the given individual should eventually be validated longitudinally by lifespan studies. For assessing the actual prognostic value of early rhythm alterations which may represent harbingers of disease, the longitudinal element is indispensable. HMOs with stable enrollees (in the sense that they change residence with a low frequency) constitute an ideal setting for the hub of an international study, tracking individuals, e.g., at yearly intervals, chronobiologically, to assess any changes in their spectral structure as a function of development, maturation and aging. This hybrid (linked cross-sectional) design (Halberg et al., 1971) should yield meaningful reference standards within a few years, both for time-specified measurements and for rhythm characteristics.

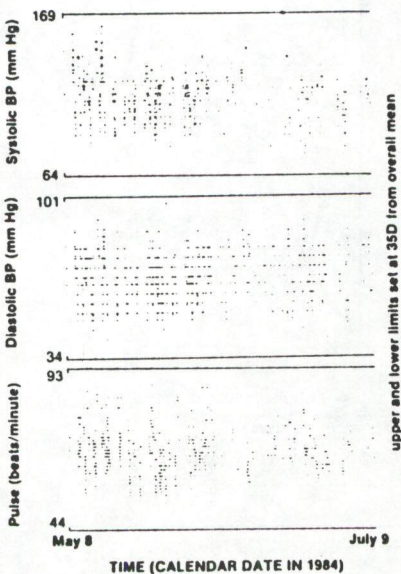


Figure 7: The large variability of cardiovascular (and many other body) functions (Halberg et al., 1988b), illustrated herein by the data of a clinically healthy woman (also providing the data in Figures 5 and 8), can be a source of false diagnoses leading to burdens in cost and suffering, reduced by chronobiologic preventive care as well as cure (chronobiologic treatment striving for the goal of being given only when needed). © Franz Halberg.

A replication of a five-year study, five years after the start of the first, should enable the tracking for another five years (twice within a decade), of populations in the age range from conception to 100 years. This follow-up of rhythms adds a new dimension to conventional tracking studies that usually need much larger numbers of participants. Even if repeated casual snapshots on a roller coaster have merits at this time (Framingham, 1971), their chronobiologic replacement is overdue. The variation illustrated in Figure 7 is best taken into account, preferably by more than the arithmetic mean, shown in Figure 8. Entering new cohorts, e.g., every 5 years, may also allow evaluation by convergence (Bell, 1953, 1954) and related modeling analyses (McArdle et al., 1988). Changes brought about by external factors may be investigated in this fashion. A case in point is the effect of dietary modifications instituted on a personal or higher policy-making level. Certainly, the womb-to-tomb study should be completed on most if not all individuals entered into it at intervals the length of which may be based in part on the first 10 years' experience.

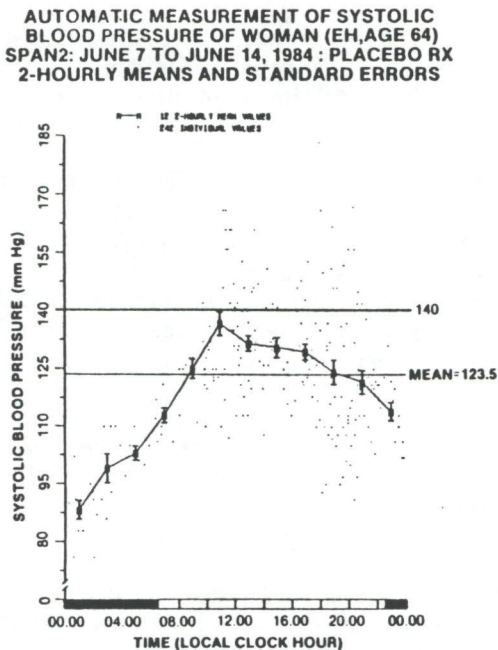


Figure 8: A clinically healthy woman may have quite a few systolic blood pressure measurements (dots) above the arbitrary dividing line of 140 mm Hg. © Franz Halberg.

The long-term feature notwithstanding, the study will nonetheless yield invaluable data each year. These (yearly and other) transverse results, rather than representing stopgap information, represent a critical complement of the purely longitudinal approach.

Times change, and 100-year-olds in another century are likely to differ from today's centenarians. A long-term goal of the study will be precisely to compare chronoanthropologic characteristics across centuries and also geographic locations. International comparisons become possible if at least comparable if not identical core designs are implemented on several continents. The health effects of concomitant social and other epidemiologically interesting changes thus could become amenable to study during the systematic collection and updating of international standards.

Special age groups. Several age groups are particularly important in terms of the prevention of high blood pressure and related diseases. One consists of the pregnant woman and her newborn baby, at a time when preventive intervention may be easy to institute and may be most helpful. Thus, one aims to study pregnant women before gene expression (for an elevated disease risk) may have taken place in their offspring. In the newborn, risk is more easily determined in the absence of interference from the host of extrauterine factors that will impinge directly upon infant, child and adolescent.

Individuals about 40-60 years of age are another special group. Sampling during mid-adulthood provides an opportunity to examine individuals, starting at an age slightly preceding the time when cardiovascular, endocrine and/or other disease conditions are more likely to become overt. Such studies of adult and aging populations may also provide reference standards in order to validate any benefits from secondary preventive intervention.

The elderly are still another group in which the mechanisms underlying the development of a given disease condition may differ from those involved in younger individuals. Rhythm characteristics change with age, in the ultradian (Anderson et al., 1989; Kane et al., 1986) as well as in the circadian (Cugini et al., 1987; Halberg, 1981) domain. Data collection on cardiovascular, endocrine or other variables at all ages is best complemented by the administration of questionnaires inquiring about the personal and familial history of various conditions for multiple disease risk assessment.

Education. The opportunity to reach school children, primarily via the educational system, should also be recognized. School children constitute captive audiences for cost-free education in self-measurements and their chronobiologic interpretation (Halberg et al., 1973; Halberg and Fink, 1981).

Lay education. For all lay groups of healthy subjects as well as patients—the enrollees of HMOs are a case in point herein—educational programs in self-help by self-measurement are highly desirable. These programs should also serve for recruiting volunteers for help in data collection and analysis.

Formal education. HMOs, by virtue of connections with University Health Sciences and with late primary and secondary education (Halberg, 1974; Halberg et al., 1973), whether these connections exist or have yet to be established, can influence teachers at all levels. The teachers in turn can be taught by an HMO's chronobiology team. The importance of academic education toward teaching 'Staying Healthy' has been emphasized by Califano (1986) and Halberg (1970). Seminars for HMO physicians on chronobiology, and in particular presentations of results from ongoing studies by HMO staff, are particularly indicated, as are newsletters both for the staff and for the enrollees.

A core project has already started in collaboration with an HMO. Ambulatory blood pressure and heart rate monitoring for 48-hour spans can be combined with the administration of questionnaires for a familial and personal history of cardiovascular, malignant, psychiatric (depression and anxiety), drug abuse and personality conditions. Means to extend such monitoring by physical and psychological examinations with a standardization and time-specification of routine laboratory work are being introduced in the framework of the Italian and European Societies for Clinical Chemistry. Taking chronobiology into account according to a multifrequency spectrum of rhythms by the specification of sampling time as a feature of international laboratory standards is already being implemented in Milan. The development of a laboratory that emphasizes monitoring and time series analysis is the long-term aim.

The laboratory may constitute a critical link in a chronotelemedicine and a chronoteleanalysis, based on expert systems, that may prescribe the proper tests at the proper times (Table 12). This may be done in the case of differential diagnostic problems that arise not only in treating sick individuals but also in screening healthy persons. Data provided by the latter population may in turn be added to the reference data base for continuously

refining and updating the reference standards. The chronobiologic laboratory's task, to prevent sickness via risk assessment, constitutes a new challenge; a clinical pathologist will be able to use time-specified reference values for the interpretation of single as well as serial samples. By taking chronobiology into account, one can complement today's health care aimed mostly at the overt disease of patients by added early, objective, quantitative and efficient focus on healthy individuals at risk, the goal of preventive medicine.

IV. HMO CONCERNS TO BE ALLAYED

Classical health care and cure delivery, chronobiologic research and practice and medically-guided self-help by education, including the physiologic self- or automatic measurement of enrollees in HMOs can all eventually be combined into an independently functional system. Thereby, three questions on some HMO-physicians' minds are answered:

1. Interference by chronobiology with other research?

Does a chronobiology team interfere with and detract funds from explicitly non-chronobiologic interests in research by a given HMO physician?

Since one of the bases of chronobiology is biometry, and since research requires estimates of the statistical significance of outcomes, a team with a nucleus of chronobiometry can support any biomedical research project, irrespective of its aims, while unobtrusively offering time as an added control perspective in the design. A number of designs and computer programs in biometry are part and parcel of chronobiology. There is also a large body of information in a variety of clinical fields that is readily available to physicians who would come to chronobiologists for support in research. Advice, irrespective of chronobiology, can be provided in terms of a protocol for chronobiologic pilot studies (Cornélissen and Halberg, in press) and data analysis by the chronobiologic team experienced in biometry as such.

For instance, once serial data are available before and after a given intervention, it becomes possible to assess the patient's response on an individualized basis as well as to summarize group results. To take the case of traditional ambulatory blood pressure monitoring, chronobiometry can provide P-values and confidence intervals to the physician interested only in whether the intervention lowered or raised blood pressure or left it unchanged, while also rendering the answer more reliable. To the physician also interested in the

dynamic structure of blood pressure change, chronobiometry can add information regarding possible effects of intervention on rhythm characteristics as well as on the mean value, even if originally the study was designed without consideration of chronobiology.

It remains up to the HMO physician to incorporate or not unobtrusive recommendations concerning timing as part of the design. Chronobiologic designs relying on more than a single timepoint are usually cost-effective and yield information on dynamic rhythm characteristics as well as on the mean value, thus uncovering effects limited to the dynamics of body function (Cornélissen and Halberg, in press). Such findings and publications can be an important dividend from any research (Günther et al., 1980; Halberg et al., 1982a).

2. Interference by chronobiology with caregiving?

Does research complicate and detract from care?

Complementary rather than conflicting roles are played by research and caregiving when these endeavors are integrated in order to improve the long-term fate of the patient, e.g., by timing treatment and/or timely intervention. For this purpose, the research group should be so organized that it supports the services of the primary caregivers while the caregivers help research in various ways, without adding substantially to their burdens, Figure 1. This is readily realized since the existing body of knowledge in chronobiology is directly applicable to patient care. In many cases, very little needs to be changed in practical terms: time needs to be recorded and/or certain interventions may benefit from being scheduled differently in time, whether it be testing for allergies, radiation or drug therapy or diet, Tables 2 and 3. Emphasis should be placed on routine home monitoring before each physical examination, thereby creating a unique data base in health. Whereas, at the outset, in a stepwise approach, the introduction of chronobiology would change the provision of health care very little, gradually, it can have great impact, in relation to screening, diagnosis, prognosis, therapy, risk assessment and even prevention, Table 4. One example is the frequently poor performance of antihypertensive treatment; systematic home monitoring can help the physician decide whether treatment is needed and, if so, to optimize the timing and dosing of its administration.

Patients monitoring their own blood pressure cannot be called guinea pigs. Their participation in research from this viewpoint is medically indicated the same way as is exercise or a certain diet,

whether the purpose of the self-monitoring be for screening or for diagnosis and treatment. In all of these cases, chronobiologic monitoring complements care-giving, rather than conflicting with care.

Benefits anticipated from the chronobiologic approach are twofold. First, health maintenance could be improved by screening for risk, followed by intervention for disease prevention and a consequent reduction of suffering, cost of care and indirect costs of absenteeism. Second, the approach will reduce the amount of medication needed, thereby cutting health care costs directly and indirectly by reducing the severity of side effects. At the same time, the data that accumulate from home monitoring and from clinical outcome in relation to timed screening and/or intervention serve for research purposes first and thereafter for optimizing clinical activities in the light of the research. Outcome analyses can be fully separated from everyday care (for those who prefer to follow their established pattern). If, in turn, some staff is willing to accept chronobiologic practices, a test of any merits or demerits to one or the other approach becomes possible in the form of outcome assessment within the HMO, without any load upon the time or activities of the clinical staff, Figure 1.

HMOs accumulating an informational data system with large numbers of reliably time-coded cases of many health-related conditions can exploit their clinical data in research when outcomes are fed-back and used promptly in the clinic. Such a system may be particularly helpful in assessing the value of a given treatment such as antiarrhythmic drugs in relation to sudden death, a condition exhibiting about-daily and about-weekly patterns (Halberg, 1984). An integrated computerized system, implemented on a large scale, would serve for a chronobiologic cost-benefit assessment of outcomes. To cite a precedent on a much smaller scale, computers today read an electrocardiogram and provide the necessary information while dispensing with the need for the cardiologist to read ECGs for many hours. The fears of cardiologists that the computer may 'overrun' them are now allayed. It is also possible to further chronobiologically 'read' (analyze) 24-hour and preferably longer records of the ECG, blood pressure, EEG, gastric acidity, temperature and motor activity, that are becoming available. Special chronobiologic software provides the necessary information at little effort and cost.

3. Too costly?

Is chronobiology a burden in the economics of group or solo practice?

As a nearly cost-free minimum, the suggestion is made here that an HMO code by time of day and calendar date every sample, e.g., of blood drawn and every procedure carried out such as an allergy test (Haen, 1988; Reinberg et al., 1969), a psychiatric test (Halberg et al., 1984) or a treadmill test (Halberg et al., 1988b), since rhythms characterize the outcome of these procedures. Once outcome studies are optimized by scrutiny and exploitation of the merits to timely and timed intervention, chronobiology represents an opportunity in cost control by reducing both over- and under-treatment and by recognizing and lowering the risk of developing disease, an approach preferred to the across-the-board rationing of care and/or to a presumed dilution of quality in a conventional national health care system. Serial self-measurements of vital signs and their chronobiologic summaries can eventually be prepared for an individualized reference standard by the healthy subject and also by many patients, e.g., before each physical examination, e.g., for high blood pressure or before surgery (Cavallini et al., in press; E. Halberg et al., 1981a).

If the HMO shows a broad interest in chronobiology, for instance with the aim toward a preventive approach to health care, then chronobiology may become immediately applicable, as, for instance, by routine around-the-clock manual or automatic blood pressure monitoring, analysis and interpretation (Bakken and Halberg, 1988; Bakken et al., 1987; Halberg et al., 1987b, 1989a, in press). Results from research carried out somewhat separately from the clinics could be regularly made available in a newsletter to HMO physicians. On this basis, recommendations could be made for specific applications with regular reports on statistics assessing any change in outcome by the introduction of chronobiology. This approach offers the advantage of being very flexible both in terms of acceptance of a chronobiologic practice and in terms of specific areas of application. The latter would depend on the physicians' interest and involvement with the chronobiology team and on the extent of improvements achieved by chronobiologic considerations in health care. Just like microscopy in space, chronobiology, a microscopy in time, readily provides novel information, once the need for such information is realized and the service is requested in practice, rather than being relegated to research. As do clinical and anatomic pathology, so can chronobiology provide a service. A MESOR-hypertension or a core temperature MESOR elevation are objective refinements as compared to 'hypertension' and fever above some consensus-derived limits. A deviant circadian amplitude of blood pressure or an abnormal breast surface temperature rhythm indicating an increased risk of breast cancer provide information that is novel in kind and perhaps useful in practice. Eventually, a

chronobiologic research team could develop a physiologic self- and automatic measurement and interpretation unit with an educational component, that may constitute a halfway house unit of clinicians, researchers and volunteering enrollees, helping to implement what is research today and may become good practice tomorrow.

V. A POTENTIAL ROLE OF HMOs IN EDUCATION

Califano (1986) writes that the likelihood of recovery is 75% if an alcoholic '... has a job or task in life and joins Alcoholics Anonymous'. Hence, the physician must spot alcoholism, alcohol abuse or exposure to alcohol, especially in children and teenagers (and preferably as a research task, already in the baby). The lack of training of medical students to make the right diagnosis may lead to the wrong treatment that may interact with other drug abuse to render a grave problem much worse. By combining chronobiologic alcoholism-oriented research (Hermida et al., 1986), one might be able to recognize the earliest tendency toward alcoholism. This is a chronobiologic task since tentative time-dependent endocrine classifiers, notably but not exclusively circulating dehydroepiandrosterone sulfate, have been identified and may serve as risk indicators for a personality prone to alcoholism and as clues for corrective intervention (when a certain risk elevation may depend upon a time-dependent reduction in circulating hormones, a condition possibly corrected by a substitution treatment for risk lowering [Halberg, 1983]). The age-dependent decrease in circulating DHEA-S as well as the rhythms must, of course, be taken into account in such risk assessment.

For HMOs with physicians on salary, there is no longer an incentive to overtreat and every reason to focus on prevention and health maintenance. This point is made rather candidly by Califano when he emphasizes 'For most doctors, the bucks are in treatment of disease, not in its prevention or in health promotion.' In removing the economic motive and in showing the possibilities for prevention, a chronobiology team can serve the HMO in securing greater health benefit for the enrollees. In the U.S. in 1987, the direct and indirect costs of blood pressure-related diseases and of alcoholism, targets of chronobiologic care and research (Halberg, 1983), were estimated to have totalled U.S. \$54 billion (Halberg et al., 1988b) and \$117 billion, respectively (Holden, 1987).

The merits of education, providing dividends in the long run, are illustrated by Califano (1986) for the case of Chrysler, a company pushing an education program for its employees and retirees, and

setting an example for HMOs and everybody else. In addition to smoking cessation, Califano cites five other core elements: weight control, nutrition, exercise, stress management and blood pressure control. One of us had much earlier advocated chronobiologic health literacy (Halberg, 1970; Halberg et al., 1973) as the most effective and, if implemented in schools, cost-free way (except for the purchase of monitoring tools, e.g., in lieu of other high school science equipment) to schedule exercise (Crakes et al., this volume; Halberg et al., 1988b) to improve nutrition (Halberg, 1989) and to manage emotional and physical burdens as well as to screen for a deviant blood pressure (Halberg et al., 1987a, 1988b). The programs implemented in the 'Chrysler story' (Califano, 1986), can only gain from a chronobiologic dimension (Halberg, 1970). Califano emphasizes that the first step is to recognize the difference between health care and sick care.

This is indeed par excellence the task of chronobiology, which can compare rhythm alterations occurring within conventional reference limits, when homeostatic approaches fail. Califano further admonishes physicians that they '... have by and large neglected their responsibility in health promotion and disease prevention. To get costs under control, doctors must focus on keeping us healthy. That is the work we should, in the first instance, train and pay them to do' (Califano, 1986). HMO staff members may try to persuade universities to live up to teaching this task. Whether or not they succeed immediately (it may be a slow process since nobody wants to give up teaching time or to add to the curriculum), there is a splendid opportunity for HMOs to participate in or even to shoulder the chronobiologic teaching task, to cut costs while improving the quality of care.

VI. CHRONOBIOLOGIC ASSESSMENT OF OUTCOME AND OPTIMIZATION

Computerized practice monitoring and chart reviews, advocated, among others, by George C. Halvorson (1988), can provide a dividend by focus upon the details and outcomes of timing by a relatively small investment (into the reliable time coding of data). This expense of coding and checking entries (required for cost-accounting) may yield a substantial benefit, Tables 2-4. The systems are already in place, but they have to be transformed into chronobiologic data bases. After a rigorous check of the quality and reliability of information on timing, the overall data review and the evaluation of all-important outcomes can only gain from a chronobiologic perspective. To illustrate the potential benefit of timing, the 2-year disease-free survival from the radiotherapy of certain advanced perioral cancers has been doubled by treatment

at the peak of the circadian rhythm in tumor temperature (Halberg and Halberg, 1984). In this case, a non-invasive marker rhythm was available to time treatment, namely perioral tumor temperature. Rhythms in high energy phosphate metabolism, revealed by electromagnetic resonance spectrometry (Halberg E. et al., 1989) remain to be assessed in tumors as potential treatment timing markers.

The importance of a spectrum of rhythms as phenomena that can tip the scale between life and death is revealed by the detection of differences in the incidence of stroke as a function not only of time of day, but also of time of week and of calendar date. This recent finding is made notwithstanding the lumping of people with different genetics, different past history, and different schedules under uncontrolled environmental conditions. A simple tabulation of deaths from different causes of stroke allows further the demonstration of different patterns (Johansson et al., 1989). Thus, along the 24-hour scale, stroke from subarachnoid hemorrhage peaks in the evening, whereas stroke from other causes does so in the morning. Patterns that are statistically significant also emerge along the scales of a week and of a year; again, they differ for strokes of different causes. A number of mortality and morbidity rhythms (Muller et al., 1989; Reinberg et al., 1973; Smolensky et al., 1972), previously shown under the controlled conditions of a laboratory, have thus been reproduced in real life. Myocardial infarction as well as strokes, peaking at certain times of day, make headlines. In the case of myocardial infarctions, it has also been shown that some patterns are altered by drugs such as β -blockers (Muller et al., 1989). Such studies provide clues as to the mechanisms involved in increased time-dependent (chrono)risk. Usually, a multifactorial constellation contributes to the undesired outcome (morbidity and mortality); it is then the aim of chronobiologic research to lower such factors, once they have been identified, as measures toward disease prevention.

More specifically, the pay dirt from looking into morbidity and mortality statistics has been to establish that there are dramatic about-daily, -weekly and -yearly patterns that are reproducible and can be documented with samples exceeding, in some cases, 430,000 human deaths (Reinberg et al., 1973; Smolensky et al., 1972), as a caveat for the practitioner to keep rhythms in mind. By changing focus from the dead to the living, once an HMO's computer systems are programmed with consideration of chronobiologic concepts and methods, it will be possible to see whether certain types of treatment change not only the percentage of survivors but also the time patterns of morbidity and

mortality. Thereby, one would learn which treatment timing had the most favorable outcome; new clues as to underlying and possibly correctable mechanisms of time-dependent risk, chronorisk, will be found. From non-random time patterns of morbidity as well as mortality as first time-dependent outcomes, one may obtain the clues for achieving prolonged disease-free survival in a variety of conditions, from cancer to cardiovascular disease.

Indeed, outcome studies should automatically scrutinize, on a day-to-day basis, the effects of timing of clinical procedures (such as treatment administration) and relate them to changes in response variables such as marker rhythms. A recent example of the merit of as-one-goes follow-up of outcomes relates to the ongoing Cardiac Arrhythmia Suppression Trial (CAST), sponsored by the National Heart, Lung and Blood Institute (NHLBI). In this multi-center, double-blind, placebo-controlled trial designed to determine whether antiarrhythmic drugs could reduce sudden cardiac death in (post-myocardial infarction) patients with ventricular arrhythmias, NHLBI suspended the use of encainide and flecainide before the trial was over. This decision was prompted by the fact that the safety monitoring board, examining data on 1500 patients treated an average of 10 months, found that about 2.5 times as many patients given encainide or flecainide had died as those given placebo. Results were similar for both drugs and in most subgroups of patients, such as those with ejection fractions of above or below 30 (FDA, 1989). Pertinent to the importance of timing the administration of cardiac drugs is the prominent multifrequency spectral structure of cardiac arrhythmia as well as the extent of day-to-day variability of its circadian and other rhythm characteristics, which should prompt more than a conventional reading of a 24-hour ECG (Carandente O. et al., 1987). Far beyond the scope of cardiac arrhythmia, it does not follow that all rhythm alterations are undesirable. While drugs that reduce cardiac arrhythmia may increase (by not necessarily related mechanisms) mortality, some degree of rhythm alteration may be desirable in some aspects of the circadian immune system. Scrambled circadian rhythms may reduce cancer incidence in several laboratories (Carlebach and Ashkenazi, 1987; Halberg et al., 1986b; Kort et al., 1982, 1986).

VII. THE MERIT OF OPPORTUNISTIC CHRONOBIOLOGIC TRIALS

Clinical trials are being re-evaluated. From a statistical viewpoint, random assignment of treatments is an essential feature of experimental design in general and clinical trials in particular. As pointed out by Armitage (1982), randomization is entirely

compatible with medical ethics in circumstances when the treatment of choice is not clearly identified. The need to monitor outcomes of large clinical trials is, for instance, illustrated by the case of the antiarrhythmic cardiac drugs encainide and flecainide (FDA, 1989). In order to avoid vagaries due to small sample sizes, it has usually been recommended to wait until completion of the study to evaluate outcomes. From an ethical viewpoint, this opinion is not tenable. Sequential tests have been proposed and constitute a substitute approach, not only in research (Berry, personal communication), but also in actual medical practice.

In patients with convulsive disorders (Johnson et al., 1959), fluctuations in seizure frequency are common. The problem of the significance of these fluctuations is germane to the clinical evaluation of the course of the disease and particularly to treatment as well as research on anticonvulsant drugs. Accordingly, sequential testing may be used, among others, in the care of certain (but not all) patients with convulsive disorders. Such tests serve as monitors of the presence or absence of a reduction in seizure incidence. Thus, seizure frequency data need not be examined only at intuitively chosen, usually long intervals. The check for the presence or absence of changes in seizure incidence can be made frequently, if necessary daily, by means of sequential testing. Such testing is so simply done and interpreted that its day-to-day performance may be delegated to non-professional personnel. Thus, the test is automatic as far as the physician is concerned, and cost-effective.

The procedure is graphical (Johnson et al., 1959). In simplified forms, it may be set up with minimal arithmetic and thereafter it is carried out with no computation. The tests have limitations and are not always applicable. When pertinent, however, sequential testing may provide more objective, rather than merely intuitive, decisions as to the significance of changes in seizure incidence. The risk of erroneous decisions is largely predetermined and reduced to practical limits.

Interest in clinical trials has also been renewed from ethical, legal and psychological viewpoints. Miké et al. (1981) address the need to provide as much information as possible in the consent form that should be written in an easily understandable language. Issues such as the existence of a placebo group in the study and background information underlying the aims of the study should be conveyed to the volunteers. These authors also stress the need to incorporate questionnaires enquiring about psychological issues in order to make it possible to evaluate any improvement to life quality. This aspect is particularly valuable for phase I trials aimed at testing, on terminally ill patients, experimental

procedures that have only a marginal chance of success in prolonging life and that may be associated with potent side effects.

Another issue gaining in interest is the reevaluation of the merit of P values, as but one of many aspects in the transition of medicine from art to science. As noted by Ware et al. (1986), P values should be considered in making decisions about the usefulness of a treatment but form an inadequate sole basis for such decisions. In addition to reporting the actual P value (rather than a range), these authors recommend providing summary statistics for the data, to state whether the test is one-sided or two-sided, to list confidence intervals, to discuss any effects of selection or multiplicity and to report the power of the tests. The need to provide confidence intervals is also stressed by Evans et al. (1988). In an editorial to the *British Heart Journal*, these authors note the trend towards estimation and away from hypothesis testing. They rightfully point out that many published studies do not seriously consider the possibility that an intervention has no effect. If so, the appropriate question is not 'Does the intervention have an effect?' but rather 'How great is its effect?'

Concerning the matter of estimation vs. hypothesis testing, we have emphasized several merits of chronobiologic data series (Halberg and Bingham, 1987). Given such series, it is possible to obtain P values and to derive confidence intervals for each estimated parameter of changes occurring in the given individual as well as among groups. Moreover, regression diagnostic tests are used to check on the validity and reliability of the estimates. Thus, in medical practice, one can compare serial data before and after a given treatment for the given patient.

The merit of individualized P-values, in medical practice, as a necessary but not as the only condition for decision making is obvious, as is the need to assess both clinical and statistical significance. This issue is addressed by Feinstein (1985). He discusses the use and abuse of concepts of significance in medical population studies, and points out that generally and wrongly, statistical significance is regarded as being both quantitative and stochastic in nature, irrespective of whether or not the findings are 'impressive enough'. Due to the nature of statistical tests, however, statistical significance can be achieved by a large difference or by a large number of data and/or a small dispersion of the data. A small difference in outcome (too small to be quantitatively significant), for instance in the case of an antihypertensive response, may become stochastically significant if the number of data is large enough and/or if the dispersion is small enough. The sole examination of P-values then completely disregards the question of quantitative significance, which should

have precedence over stochastic significance. What appears to be sole stochastic significance, however, may regain clinical significance when the difference in outcome is not taken at its face value, but rather as a descriptor of possible linkage between two physiologic effects. For instance, low-dose aspirin may affect, via prostaglandins, both blood pressure and platelets. The effect upon blood pressure may be very small; nonetheless it will be clinically significant if it identifies those patients who may or may not benefit and those who may even suffer from this treatment from the viewpoint of its anti-platelet activity (Ferrazzani et al., 1989).

In a satirical paper on statistics as practiced in medical journals, Salsburg (1985) notes that the emphasis on hypothesis tests and on arbitrarily specified alpha levels has distorted the interpretation of clinical trials, with the result of a perceived failure of these studies to influence medical practice. He also points out that for the practicing physician, there is little value in knowing that a given treatment is significantly better than placebo. More pertinent questions proposed by Salsburg are: 1) If a given treatment is effective, how long will it take for the response to manifest itself and what can be monitored to know whether such a response has occurred?; 2) How can patients most likely to respond and patients most likely to suffer adverse reactions be identified?; and 3) If an adverse reaction is going to occur, what are its early manifestations and what is the general pattern of the hazard function?

With these questions, Salsburg identifies several important issues that chronobiometry can help resolve with the additional consideration of the time dimension (Cornélissen and Halberg, in press; Ferrazzani et al., 1989; Halberg and Bingham, 1987; Halberg et al., 1988b). These issues are the gain from a given intervention, the need to individualize the assessment of a patient's response to a given intervention, and the benefits from monitoring marker rhythms.

The systematic recording of time combined with the computerization of all relevant clinical information offers rich possibilities to conduct opportunistic chronobiologic trials. Such trials aimed at assessing outcomes as a function of the timing of a given intervention would be largely and naturally randomized at the outset. Since they would involve only the summary of existing information, they would be ethically acceptable. By the nature of a periodic summary of outcomes, the design would be sequential. Whenever trends are identified, further analyses could be easily conducted to test for possible sources underlying the observation and to examine the extent of reproducibility of the results in

different subgroups of patients. Accordingly, changes in clinical practice can be recommended. This approach resembles that of quality control monitoring, used widely and for a long time in the world of industry.

VIII. CONCERNS ABOUT HEALTH CARE QUALITY, EQUITY AND COST

The quality and cost of care are compared given different scenarios and alternative futures for the health care system in 2010 by Meyer and Lewin (1987). Some common trends emerge despite the large differences in approach. Likely scenarios considered are continued growth, decline and stagnation, a disciplined society or a transformation. The common trends include the role of technology and expert systems to monitor health care and promote self-care. Emphasis is placed not only on a better medicine but also on better lifestyles. A key element is not listed in these scenarios: namely the role of education to achieve better lifestyles and to self-measure marker rhythms in variables such as blood pressure, heart rate and peak flow that may yield, for specific patient groups, motivating results as a feature of self-help in health care. Such education allows the cost-effective collection of time series instead of casual snapshots and hence the implementation of chronobiologic risk detection and timely intervention, selectively in those who need it.

Rationing health care has its advocates (Blank, 1988; Callahan, 1987). It is common sense, however, to emphasize preventive health care for reducing both suffering and cost (Halberg, 1970). Increasing investments into conventional trends in health promotion may not be enough; more is needed than the conviction that even if we never reach perfection, we shall make some progress by cost-cutting and equity considerations (Blank, 1988; Califano, 1986; Durenberger, 1986; Feeny et al., 1986; Fein, 1986; Meyer and Lewin, 1987; Reece, 1988). One needs more than increased efficiency, competition and consumer choice, although such conditions are important. The prospective payment system, e.g., of Medicare and of HMOs, has rightly aimed at solving an important aspect of care, namely its cost; cost considerations also underlie the issue of switching from primary 'sick' to 'health' care (Califano, 1986). An HMO cannot afford to ignore the progress in chronobioengineering (Halberg, 1987a, 1987c) in order to raise the quality of care while cutting costs.

Cost and medical care problems are inseparable from chronobiology, required for a rigorous evaluation of the clinical effectiveness and economic efficiency of new techniques before their final adoption. Costly instrumentation for drug

administration, if it is to improve performance within the health care system, may be used in research to develop optimal schedules that can subsequently be used broadly in order to time conventional treatment cost-effectively. A case in point is the administration of cyclosporine to prevent graft rejection. The expense for cyclosporine (estimated by Blank [1988] to be from \$4 to \$10,000 per year for a patient with a heart transplant) may be reduced simply by timing the administration of the drug, i.e., by giving the drug only as the evening dose, for a diurnally active patient (Cavallini et al., in press).

Randomized controlled clinical trials constitute another area wherein chronobiology can make an impact. Because of neglect of rhythms, the error of using conventional criteria for entry is almost certainly very large. Accordingly, the outcome of trials will be highly questionable, as seen in the case of a series of expensive studies on the treatment of mild blood pressure elevation (Halberg et al., 1988b; Wilcox et al., 1986). Almost certainly, a substantial share of the several billion dollars spent on antihypertensive drugs each year in the USA could be saved if 48% of 1943 individuals diagnosed as mildly hypertensive are cured within 3 years by a placebo (Halberg et al., 1988b, 1989a; Little et al., this volume). Another large study, the (U.S.) Hypertension Detection and Follow-Up Program (1979, 1982), involving 10940 individuals, reported in the control group a corresponding percentage of 47% cures; the same percentage of 47% of a sample of about 180 'hypertensive' patients were simply taken off medications at The Menninger Clinic (Topeka, Kansas), '... and with no other treatment, they remained normotensive' (S.L. Fahrion, personal communication; cf. also Halberg et al., 1988b; Little et al., 1989). The reduction in side effects and in unjustified discrimination when a healthy person is labelled as sick are also noteworthy (Halberg et al., 1988b).

Manton (Schramm, 1987) emphasizes the need for focus upon high blood pressure as part of standard medical practice, notably in the elderly. He also points to the difficulties encountered in building incentives for primary prevention at younger ages; for both these age groups, chronobiologic health literacy and, again, self-, if not automatic measurement may reduce cost, keep up motivation, and provide the necessary health benefit. Unless this is achieved, prevention will indeed be more expensive than appears at first glance. Without self-help, by self-measurement to cover odd times as well as to reduce cost, endeavors in the treatment or prevention of high blood pressure were disappointing. It is commonly and erroneously assumed that the test for high blood pressure by care givers is simple and cheap and entails no risk. (The risk of misdiagnosis is hardly trivial, however.) The consequences of

high blood pressure, stroke, heart and kidney disease and blindness, to cite just a few examples, are expensive. It would appear to some that, accordingly, one cannot go wrong in advocating that blood pressure measurements be made every year or every other year on the seemingly healthy population as a whole. Rightly, critics point out that this approach is not cost-effective. Indeed, the yield of such tests, notably when they are done casually, is quite modest relative to the costs of screening, done by health professionals. Critics will add that once high blood pressure is validated, there are substantial continuing costs for checking the effect of treatment.

Most of these costs can be reduced if not eliminated when the individual to be screened is educated in chronobiology and in self-measurement or automatic measurement when this is needed, and when self-testing is systematically planned, according to early determinations of risk status, rather than by a shotgun approach. Once chronodesms are available for the given individual, a few measurements suffice for monitoring the healthy subject subsequently at intervals dependent on the individual risk assessment. The feasibility and potential benefits of this approach have already been demonstrated in schools in Arkansas, Connecticut and Minnesota (Halberg et al., 1973) as well as in Florence, Italy (Scarpelli et al., 1987). Weinstein and Stason (1976) indicate that the saving in medical expenditures, because of fewer strokes and heart attacks, covers less than one-fourth of the costs of screening for moderate and severe 'hypertension'. Such statements will have to be reconsidered in a chronobiologic context of medically-guided self-help in blood pressure assessment.

Cholesterol treatment also has implications in dealing with high blood pressure (Dzau, 1989). Conceivably, some of the merits of a treatment with agents such as diuretics or beta-blockers, given to lower blood pressure, may be reduced by possible undesirable effects of such agents upon lipid metabolism. It is clear that both desirable and undesirable effects can be influenced by timing; for the case of diuretics, an undesirable effect, namely kaluresis, can be reduced by timing (Halberg E. et al., 1987).

Even the time of eating can be optimized chronobiologically. The utilization of calories differs as a function of timing (Halberg, 1989). In a 1-week study, a given individual consumed a single daily meal (2000 kcal) 12 hours after awakening. Thereafter, for a similar span, the same daily meal was consumed within the first hour after awakening. Some subjects started on 'breakfast-only', others on 'dinner-only'. There was a marked shift with meal-timing in the time of high values for plasma insulin and glucagon

and for serum iron. Concomitantly, the rhythm in urinary cyclic AMP excretion, also tested on the schedules with a fixed energy intake, with a change from 'breakfast only' to 'dinner only', did not shift appreciably in circadian timing. When only breakfast was consumed, the glucagon and insulin rhythms are very similarly timed, and their confidence arcs overlap. By contrast, when only dinner was consumed, there is no overlap between the confidence arcs. Tests indicate that the internal timing of glucagon and insulin is different when a single meal is consumed as breakfast vs. dinner, while the sleep-wakefulness schedules are kept as similar as possible.

In a second study, the single daily meal was unrestricted as to the choice of food and the number of calories consumed, for successive 3-week spans, as breakfast-only or as dinner-only. The most consistent finding was made with respect to body weight. Whether or not the total energy intake per meal at different circadian times was controlled, there was again a relative body weight loss on breakfast-only as compared to dinner-only. This relative body weight loss, however, was smaller when the subjects ate whatever they liked (on the average, less than 2000 kcal); they lost more weight when they ate more, in the study with a single breakfast-meal or dinner-meal, when the subjects ate a precisely fixed (2,000-kcal) meal, which they did not like ($P < .05$). Therefore, in addition to the effect of total energy intake, an influence of meal preference was also apparent.

If a calorie at breakfast differs from the same calorie at dinner, in terms of its utilization (Halberg, 1989), so do drugs. Banta and Gelijns (Schramm, 1987) indicate that although drugs have saved many lives, they do present problems, referring to the case of diethylstilbestrol during pregnancy which has brought about vaginal cancer and other complications in offspring exposed to the drug in the womb. Chronobiology may have uncovered, in the form of altered circadian, circaseptan and circannual blood pressure rhythm characteristics, the dangers of betamimetics given for spotting (Halberg et al., 1988c); instead of leading to malignancy, these drugs may enhance cardiovascular disease risk (Tarquini et al., this volume) and may also result in a learning deficiency (Hadders-Algra et al., 1986), a possibility deserving more chronobiologic research, as indicated above.

Public polls rate medical research as the highest priority for national research support; over half of those polled believe that prevention of disease should be emphasized (Blendon and Altman, in Schramm, 1987). Feigenbaum (Schramm, 1987) writes from society's viewpoint that an optimal system of risk-bearing assures first that 'riskiness' is reduced in a least-cost fashion to a point

where the cost of prevention does not exceed the cost of treating the disease. Chronobiology might serve this aim by combining self-measurement or the self-implementation of automatic measurements for diagnosis with a reduction of the amount of needed medication by the timing of its administration, thus achieving a reduction in the cost of both monitoring and drugs. The feasibility of educating the patient to adjust dosing and timing has been amply illustrated in the case of patients with insulin-dependent diabetes. Expert chronobiologic systems are being developed to blend timing with dosing, manually or by the use of implantable pumps, while they also serve to schedule meal times and activities of diabetics or 'hypertensives' (del Pozo et al., 1988; Gallardo et al., 1987).

Without chronobiology, without inferential statistics, health care has not become an exact science which objectively assesses outcomes in response to every problem. The mind, in many ways, in the form of effects from bedside manner and placebos, plays a critical rôle. Fein (1986) writes: 'Medical care can be produced in many different ways with different combinations of resources with different proportions of workers and types of capital'. We may add, what is relatively easy to implement and can yield large returns, medical care can also be produced with a different timing, primarily in terms of the timeliness of intervention early in the natural history of a condition and, when appropriate, by the taking into account of the body's time structure (Halberg, 1970, 1983).

Fein (1986) describes today's health care systems as inefficient and concludes his agenda for action and for doing something about health care budgets by writing that much will depend '... upon whether enough of us care enough to work at translating concepts of decency, humaneness, cooperation, universality and justice into actions that would protect all members of the American family [and we would add, in a broader perspective of humanity and its ecosystem]. Conveying to patients warmth and caring may also have healing capabilities, as have exercise, the presence of a mate, or a pet for elderly persons living alone, and a pleasant environment, or other features, all of them considered in what one of us (EB) has described as cyberphysiology. The derivation from kybernet(es), 'the helmsman', is shared with cybernetics, described (by Webster's Third New International Dictionary [1965]) as 'the comparative study of the automatic control system formed by the nervous system and brain and by mechanico-electrico-communication systems and devices (as computing machines, thermostats, photoelectric sorters)'. Cyberphysiology is defined by one of us (EB) broadly as the conscious self-coordination of

usually autonomous body functions. That a positive attitude and any and all factors reinforcing it add to the quality of life, including the area of neuroimmunomodulation, deserves emphasis. Objectively documented applications by chronobiologic methods seem promising since modulation depends heavily on rhythmic interactions: the feedsidewards (Carandente F. et al., 1988; Halberg, 1983; Sánchez de la Peña et al., 1983a and b). These feedsidewards constitute testable neuroendocrine mechanisms. It is important to assess such mechanisms when, as a function of rhythms with several frequencies, feedsidewards account for the difference between a stimulation or inhibition of a cancerous growth (Halberg, 1983; Halberg et al., 1988b).

To turn back to Fein (1986), 'At stake is not only our health care system, but the very nature of our society.' One could paraphrase Fein and say that since rhythms are known to characterize every aspect of human body function, and since we need these ubiquitous rhythms for controls in a scientific medicine, 'much will depend upon the incorporation of chronobiology', as a feature of scientific decency, scientific humaneness and scientific cooperation, in order to control costs, ensure equitable access to health care and still raise quality (Kane and Kane, 1985). Trends toward improvement in quality of care include components such as a 'hospital on the wrist', preferably an implantable one that would function from womb to tomb, linked to centralized expert systems.

Scientific and cost-effective medicine both require that one neither overtreat nor undertreat—to cite Halvorson (1988), that one 'provide every single bit of needed care—and no unneeded or excessive care'—and that one focus on lowering risk, the chronobiologic substitute for the choice of good risk groups. To follow up on Halvorson's line of thought, one may aim at placing everybody into a good risk group by recognizing and then lowering risk chronobiologically.

IX. CHRONOBIOLOGIC AIMS

An efficient system of risk bearing aims at risk avoidance (Schramm, 1987), whether a system looks on health as a duty to fulfill or as a privilege that the state makes available free of charge or as a commodity to be bought (Halberg, 1970). The lowering of the risks of developing disease presupposes chronobiologic risk detection, i.e., the study of any harbingers revealed by alterations of rhythmic changes within the 'usual range' of vital signs and/or clinical chemical laboratory values. For too long, the words 'physiologic' and 'random' have been used

as exact synonyms (Halberg, 1953). The time has come for a preventive public health system that exploits the rhythmic changes within the 'normal range' that are the fabric of all life. Modern technology can implement what a decade or two ago proved to be too demanding of self-discipline (Halberg, 1970; Halberg et al., 1972, 1973). There is no longer a need for a negative definition of health based upon the absence of disease and/or upon values judged as acceptable (or unacceptable), since they are within (rather than outside) a time-unspecified arbitrary range of usual values. Such qualitative endpoints can be replaced with a positive, quantitative and individualized assessment of rhythm characteristics to gauge health. Even the engineering aspects of a health card, seemingly a utopia not so long ago for many with but few exceptions (Halberg, 1970), are solved. On such a card, the last original time series, e.g., of blood pressure, can readily be stored, with earlier rhythm parameters, and the card can be updated by monitoring at appropriate intervals. This seems to be worthwhile, if risk assessment by rhythm characteristics works when the conventional approach by casual measurement fails (Halberg et al., 1988b).

The introduction of chronobiology into an HMO can bring dividends in preventive as well as curative health care. The introduction of ambulatory chronobiologic monitoring before and after surgery constitutes another example. The dynamics of vital signs during the operation can then be assessed in the light of prior information on the given patient. Post-surgical automatic physiologic monitoring may detect rhythm alteration as an early sign of a nosocomial infection and may save the cost of hospitalization after surgery and of rehospitalization prompted by the occurrence of high fever (Halberg E. et al., 1981a). The self-monitoring of peak expiratory flow in relation to asthma (Halberg, 1987b) or environmental pollution (Stupfel et al., 1977) may also benefit from chronobiologic designs and analyses. When to treat with corticoids and oncostatics may also be exploited in an HMO's routine. More generally, if the treatment times are recorded and the attempt is made to treat the patient at comparable clock-hours (until marker rhythmometry becomes available), much useful chronobiologic outcome research becomes feasible. To amplify on other examples, work on a gestational cardiovascular disease risk index, as a tool for testing endeavors for the prevention of eclampsia and for the lowering of infant morbidity and mortality as a short-term result, seems reasonable. A related goal is to strive for a neonatal cardiovascular chronobiologic precocity index of the risk of developing degenerative cardiovascular disease (Halberg et al., 1986a, 1988b). A decision for work along these lines is akin to that made in the 50s by the then-National Foundation for Infantile Paralysis. A choice was required between support of

work on a vaccine or on better iron lungs; a decision was made for prevention in favor of a major effort in treatment. The analogy between a decision for support of chronobiologic work toward the prevention of cardiovascular disease and the decision for work on a polio vaccine (rather than a sole investment into treatment, be it of degenerative cardiovascular disease or poliomyelitis), need not stop here. The analogy can be carried further. The poliomyelitis virus had to be grown in tissue before development of a vaccine could be initiated. Actually, the Nobel Prize in 1954 was awarded to John F. Enders, Thomas H. Weller and Frederick G. Robbins for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissues.

For the case of the prevention of cardiovascular, oncologic, emotional and other civilization diseases, there is also a requisite, even if it is along a different technical line. The current tasks are to scrutinize the merits of already identified workable indices, whereby the risk of the development of a high blood pressure or of other conditions later in life can be assessed as soon as possible after birth (if not during fetal development) to indicate those in need of primary prevention (Halberg, 1983), Table 12. The same line of thought applies to the exploitation of the finding of endocrine classifiers of a tendency toward alcoholism and particularly of the risk of developing breast or prostatic cancer, among other conditions (Halberg, 1983; Hermida et al., 1985, 1986). With respect to each of these civilization diseases, there is the long-term goal of an early detection of risk elevation as the first step toward prevention. This step is particularly pertinent to HMOs, yet is also within the scope of government funding.

It is a national or, rather, international task to collect chronobiologic reference values for risk assessment. Government-supported studies with chronobiologic designs have accordingly been implemented around the world. A 6-city study in Italy was supported by the Italian government and has provided reference data for blood pressure and heart rate on men and women ranging in age from 20 years to old age (Scarpelli et al., 1988). A study supported by the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute of the U.S. represents one core of the study at Group Health Inc. This work is intended as the nucleus of a lifespan study planned in conjunction with a similar study at Yamanashi Medical School in Japan and several other locations.

If HMOs can attract additional such grants, further improvement (by research) of the delivery of care will be feasible once the results of in-house and international research are regularly disseminated, first orally and as fliers and eventually as reprints of

Table 12

Kinds and times of endocrine sampling recommended for further tests of multiple risk assessments

Season Time-specified hormonal determination

High blood pressure:

Summer	TSH at 08:00 (IND) + Aldosterone at 00:00 (IND) or + Cortisol at 08:00 (IND)
Fall	Aldosterone at 00:00 or at 08:00 (IND)
Winter	Aldosterone at 00:00 (IND) + Prolactin at 00:00 (DIR) + DHEA-S at 08:00 (IND)
Spring	TSH at 00:00 (IND) + LH at 08:00 or TSH at 08:00 (IND) + Aldosterone at 09:40 (DIR) or + E1 at 08:00

Breast cancer:

Summer	Insulin at 00:00 (IND) or E1 at 00:00 (IND) or E1 (IND) + TSH (DIR) + Aldosterone (IND), all at 08:00
Fall	Prolactin at 00:00 (IND) or Prolactin + E2 + T3 (IND), all at 08:00
Winter	17-OH progesterone at 00:00 or Prolactin (IND) + Cortisol (DIR) + T4 (IND) + 17-OH progesterone, all at 08:00
Spring	Insulin at 18:40 (IND) or T4 at 09:40 or LH at 09:40

Expansive personality (possibly related to alcoholism and drug abuse):

Summer	DHEA-S at 12:00 (IND)
Fall	DHEA-S at 00:00 (IND) + Prolactin at 00:00 + LH at 08:00 (IND)
Winter	DHEA-S at 08:00 (IND) + Prolactin at 00:00 + LH at 08:00 (IND)
Spring	Cortisol at 18:40 (DIR) + TSH at 18:40 (IND)

*DIR=direct relationship; IND=indirect relationship.

§Adapted from Hermida RC, Halberg F, Halberg E (1986). Closer to a psychoneuroendocrine hemopsy? *Biochim. Clin.* 10: 1053-1066.

published professional articles. For the past 16 years, clinical chronobiology has had an international outlet in the journal *Chronobiologia*, which can assure prompt publication of papers refereed by peers in chronobiology as well as in classical reductionist biomedicine. Another journal in quantitative chronobiology is *Chronobiology International*. The chronobiologic approach can provide outstanding professional opportunities for clinical and administrative staff in all areas of biomedical

research, including publication. Accordingly, it may be easier to recruit and retain high-quality staff. It seems likely that through chronobiologic outcome research in practice, an HMO can assume a local, national and international leadership role in the field of a medically appropriate cost-effective chronobiologic preventive as well as curative care.

X. CONCLUSION

HMOs have the opportunity, through research in the context of actual practice, to place primary emphasis on preventive measures. These can be implemented on an individualized basis, with outcomes assessed for statistical significance by methods of chronobiometry. Chronobiologic outcome analysis also serves for both cost-containment and the assurance of quality in activities aimed at the cure of overt, notably catastrophic disease by highly technological measures. An integration of chronobiologic outcome analysis with research and education will provide professional opportunities for clinical and administrative staff in all areas from surgery to cardiology and from allergy to psychiatry. Thereby, the recruitment and retention of high-quality staff may be facilitated and the HMO, as an institution, may eventually gain formal academic postgraduate status. With appropriate staff available, an HMO can enlarge its informational data system, improve its contacts and integrate timed clinical data with information from chronobiologic research. Time-specified reference intervals will thus accumulate, Figure 9, for the interpretation of single measurements.

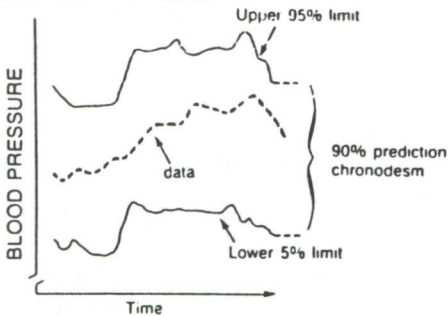
Interpretation of single measurements. Chronobiologists also provide model-dependent rhythm parameters, Figures 5 and 6, and model-independent measures of excess or deficit, Figure 10. Use of these endpoints complements reliance on classical averages of measurements, Figure 8, or reliance on single measurements, the dots in Figure 7. The choice between the homeostatic approach, ignoring the variation in Figures 5, 7 and 8, and the chronobiologic approach utilizing variation to extract novel endpoints such as those derived from the curves of Figures 5 and 6, could make quite a difference in the cost-benefit of health care.

The prevailing homeostatic approach has led to rationing, to inequities, and to a continuing waste with many false diagnoses. The chronobiologic approach has passed through the stages of concept formulation (Halberg, 1970) and limited small-scale validation (Halberg et al., 1988b, 1989c). It aims at the improvement of the cost-benefit ratio achieved by eliminating

unnecessary treatment and thus drastically cutting costs while giving every bit of possible prevention as well as cure. Against this background, illustrated herein by the approach to blood pressure, a chronobiologic unit, notably if it is integrated with an HMO in practice can play a leadership role in the continuous improvement of preventive care and also in a medically appropriate yet cost-effective cure of overt disease, with ample further research opportunities for its academically interested staff. The 'sheer fun' indicated at the bottom of Table 1 has just begun.

NONPARAMETRIC APPROACH

Excess and/or deficit: none



both present

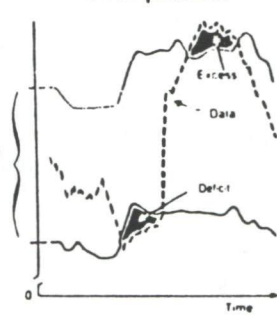


Figure 9: Chronobiologic measures include products of time and excess or time and deficit, the hyperbaric or hypobaric indices shown on the right of this figure being cases in point. Other examples relate to 'excess' in heart rate or gastric acidity. © Franz Halberg.

The major difference between traditional and chronobiological diagnostic limits is that chronobiology relies on time-varying limits established from living peers, whereas conventional limits are fixed values derived mostly from morbidity and mortality statistics.

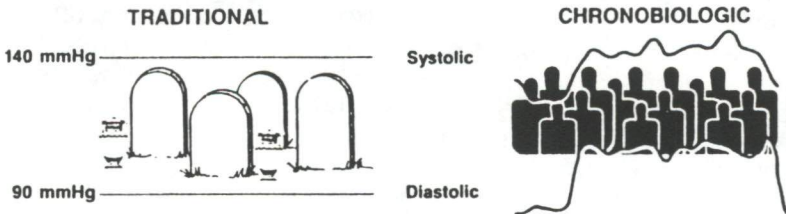


Figure 10: Chronobiologists replace the traditional consensus-derived arbitrary insofar as time-unspecified limits (shown on the left as representing the tombstones or urns of another generation); the time-varying limits derived from the data of living peers at low risk of developing high blood pressure (shown on the right) serve for the interpretation of single time-specified samples. © Franz Halberg.

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Chronobiologic Engineering

Franz Halberg

Introduction

This paper introduces the fledgling science of chronobiology very briefly, but with extensive references. It then illustrates the importance of this science for engineering aimed at health care.

Chronobiology deals with the cyclic patterns that occur in all living organisms and explores the relationships of these rhythms to prediction, prevention, diagnosis, and treatment of diseases or abnormalities more broadly. Virtually all organisms exhibit about-daily (circadian) cycles of body core and surface temperature and of chemical variables in blood, urine, and tissues. Several decades of research worldwide have established that medical diagnoses can be subject to a much higher proportion of false positives and false negatives when only single samples are taken at arbitrary times of the day instead of taking rhythms into account. Moreover, treatments (radiation, chemotherapy, and other medications) have been shown to have markedly different efficacy and safety depending upon the pattern of administration within the day.

Many persons believe that medicine stands on the threshold of a revolution in diagnosis and treatment, based on the combination of several emerging technologies, including chronobiologic under-

standing of the health effect of rhythms; availability of portable, personal, long-term ambulatory monitors of biologic variables such as blood pressure, the ECG, or EEG undergoing changes that recur spontaneously and as responses; availability of database systems to acquire and analyze volumes of data obtained from personal monitors; availability of statistical procedures to analyze and model the biologic rhythms and from them to devise optimal dosage time patterns for specific individuals; availability of portable, programmed devices to administer therapy, e.g., by physiologic rate-adjusted cardiac pacemakers or drug pumps.

These developments represent an exciting potential for engineering and health-care personnel both in research and in practical applications. The employment of chronobiologic methods in routine medical screening, diagnosis, prognosis, treatment, and, most important, disease prevention, remains a challenge to be met.

Chronobiology is not only:

1. A naked eye study in time plots of *physiologic variation*, encountered at all organization levels, from molecular over organismic to ecologic, in microorganisms, unicells, and pluricellulars, including human beings¹⁻⁶⁷;

2. The critical control in all of biology, namely the requirement that one takes ubiquitous rhythms into account once one realizes their critical pertinence to any cost-effective biologic test^{3,4};

3. An added indispensable, objective, computer-aided inferential statistical estimation of the characteristics of *biologic trends* with development and aging,⁷ including changes recurring with a broad mathematical spectrum of frequencies, the (algorithmically) validated rhythms^{4,8};

4. A generally applicable biologic methodology including, with the design of conditions for data sampling and analyses in ordinary as well as special lighting and other environments,^{17,43-46} the computer-aided *hardware and software for data collection*^{36,47} as well as for chronobiometry;

5. A set of procedures for biologic, including medical research and practice yielding improved old and new dynamic endpoints, e.g., for human blood pressure or circulating hormones. A single measure and a mean of casual measures with its standard error are the currently used endpoints. A midline-estimating statistic of rhythm, the MESOR, M, a rhythm-adjusted mean, is usually more reliable than the conventional mean based on casual samples. As

compared to the mean, the M is usually associated with a smaller standard error since part of the overall variability is assigned in *chronobiometry* to added endpoints. These are the period(s) (τ) of rhythms and, at each τ , measures of extent and timing of change, the amplitude, A , and acrophase, θ , of the fundamental τ , as well as the (A, θ)s of the harmonics of each τ that together with the characteristics of the fundamental τ , quantify the waveform^{4,41-43};

6. A basis for medical or other action based on *statistical inference* yielding probabilities (P -values) describing the reliability of findings for the given *individual*. With each endpoint of rhythm, a standard error is computed and (in view of the availability of the chronobiologic time series [rather than single measurements]), one can then test for the statistical significance of any changes—in any one or several of the rhythm characteristics—for the given individual^{63,64};

7. An approach resolving some of the individual's *interactions with the socioecologic environment*, such as physiologic synchronization or desynchronization, frequency division and/or multiplication, variance transposition or rhythm scrambling (dissimilation) in the face of complex (circadian-circaseptan-circannual) schedules in shiftwork²⁵ or transmeridian travel²⁶;

8. The resolution of *rhythms* with periods that are only an approximate (*circa* = about) match of environmental cycles, and that under conditions of isolation differ (usually with statistical significance) from their environmental counterparts, e.g., the solar day, lunar day, lunar month, and solar year. Such free-running periods, whether they are discovered after a manipulation of the environment^{17,18} or of the organism,¹⁹⁻²¹ represent a first indirect line of evidence for the heritability of *circa*-rhythms. Their periods are of about one day, the *circadians*^{3,4}; of about a week, the *circaseptans*²¹⁻²³; of about one month, the *circatrigintans*²⁴; and of about a year, the *circannuals*¹⁸;

9. A way to *quantify health positively*, inside the range of usual variation, by measuring, e.g., blood pressure rhythm characteristics and other changes such as trends (rather than indicating only the absence of unusual values [outside the "normal range"] and/or the absence of signs and symptoms of overt disease)^{60,62-64};

10. A way to assess the risks of developing diseases such as breast cancer, alcoholism, other chemical dependencies, anxiety, and cardio-, cerebro-, certain reno-, and retinovascular diseases. Constellations of rhythm stage-dependent endocrine and systemic classifiers may serve for this purpose⁶³⁻⁶⁶;

11. A paradigm of *preventive medicine*, e.g., with assessment, already in the newborn, of the risk of developing high blood pressure later in life, by the half-hourly monitoring for 48 hours of blood pressure and heart rate, followed by chronobiometry, which allows the separation by the circadian amplitude of groups of newborns with a positive versus negative family history of high blood pressure^{37,39,63};

12. A way toward *self-help* in preventive as well as in medically guided curative health care, by individuals whatever their ethnic or socioeconomic background, whether they dispose only of traditional or also of modern tools. Once data collection and interpretation with modern tools is accomplished in research, the use of traditional tools can proceed in the light of experience gained with new technology³⁶;

13. A study of *time-patterned variation in pathology*. Pertinent examples abound in human medicine, such as nocturnal versus diurnal blood pressure elevation,^{10,63} epilepsy,^{11,12} asthma,¹³ or filariasis¹⁴;

14. A basis for screening, e.g., of deviant blood pressure, such as a deviant timing or extent of change in odd-hour hypertension or circadian amplitude-hypertension^{10,63};

15. A basis for diagnosis, e.g., of Addison's disease or Cushing's syndrome by sampling blood for circulating cortisol in the morning or evening, respectively⁶⁰;

16. A basis for prognosis, e.g., of hypercortisolism,⁶¹ accelerated blood pressure elevation, or sudden, presumably cardiac death,⁶² by reliance on rhythm characteristics, rather than only a mean of casual time-unspecified measurements of blood pressure;

17. A way to optimize the utilization of calories, exploiting different effects upon body weight gain, e.g., as a function of consuming all daily calories within one hour of awakening or not before 12 hours after awakening^{4,51};

18. A dimension for classical chemical and physical treatment modes, e.g., of cancer by timed radiotherapy,⁵⁷ of high blood pressure with beta-blocking agents or diuretics,^{10,63} of asthma with corticosteroids,⁵⁸ and a host of other conditions, with timing complementary to dosing^{57,59};

19. A focus on the eminently multifrequency rhythmic immune system⁵⁸ and its earliest changes as it erodes toward diseases such as cancer or the acquired immune deficiency syndrome (AIDS). Since many individuals who carry an infectious agent, e.g., a virus,

do not exhibit overt pathology, one might speculate that one of the larger challenges of our day for *chronoimmunopharmacology* lies in the particular field of (about-daily, -weekly, -monthly, and -yearly) rhythmically recurring deficits in immunity and their chronobiologic mechanism;

20. A way to reduce if not avoid the toxicity⁵²⁻⁵⁸ of physical stimuli, such as radiation or a host of drugs. Cases in point are the cardiac drug ouabain, corticosteroids, psychiatric normalizers, anesthetic agents, and cancer chemotherapy with agents such as doxorubicin, cisplatin, arabinosyl cytosin, vincristine, cyclophosphamide, and melphalan. The body's resistance to many other kinds of agents is documented to undergo rhythmic change;

21. A set of mechanisms for multiple rhythmic interactions, the so-called *feedsidewards in biologic networks*,^{4,44,45} that substitute for oversimplified feedbacks in axes. Feedsidewards represent interactions among three or more physiologic entities and result in several orders of (a) spontaneous, (b) reactive, (c) modulatory, and (d) harmonically frequency-dividing and/or -multiplying rhythms. When these rhythms are isolated outside the body, they are referred to as α -, β -, γ - and δ -rhythms; the latter two categories of rhythms can account for directionally different yet predictably recurring effects, e.g., amplification, no-effect and attenuation, for instance, of hormone production or action⁴⁸⁻⁵⁰;

22. A study of feedsideward-derived *chronomodulation*, consisting of effects as different as stimulation versus inhibition of DNA synthesis in healthy bone by the same hormone analogue⁴⁹ or the acceleration versus retardation of tumor growth by an immunotherapeutic agent,^{43,50} in both cases as a function of the timing of agent administration;

23. A focus by *genetic engineering*, e.g., on mutants of fruit flies that lack a circadian rhythm and exhibit it again after gene transfer^{5,6} by examining the extent of reconstitution of circadians in a broader ultradian-to-infradian rhythm spectrum^{28,29};

24. A focus on *heritability*, e.g., of circadians, by studies on monozygotic twins reared apart, demonstrating that within-twin-pair differences in rhythm characteristics are smaller than among-twin-pair differences, notwithstanding the different geographic environments in which the twins were brought up and continue to live until the time of study²⁷;

25. A view of the *Darwinian evolution* of species that acquired a time structure of rhythms, in health as well as disease, including

some rhythmic changes that represent an apparent match of geophysical environmental periodicities, such as the day, month, and year^{15,16};

26. A way to look at an *internal evolution* of life on earth as a feature not only of environmental adaptation but also of integration within a microorganism, unicell, or pluricellular organism. For instance, circaseptan time structures that have no known geophysical environmental counterpart, are encountered in the time to death from natural or experimental infections,³⁰ in the time to the rejection of mammalian transplants³²⁻³⁴ (in multiples of about seven days), the blood pressure of the human newborn,^{37,39} and the response patterns to shifts of environmental cycles^{2,31,32};

27. A fledgling science in its own right with a substantial body of stimulating if as yet incomplete facts, integrated by unifying mechanisms such as cephaloendocrine and cellular feedsideways and chronomodulation, leading to new principles such as internal evolution, and offering procedures for various applications throughout human and veterinary medicine, animal husbandry, agriculture, and other fields of biology.

Chronobiology is all of these.

Illustrative Chronobiologic Challenge to Engineering Chronotherapy

The right devices for chronotherapy must be portable and miniaturized so that they do not interfere with daily life.⁶⁹⁻⁷⁸ Moreover, the devices should be programmable, so that in a day and age of real problems in compliance, one relies on modern technology rather than on the patient's discipline and memory. Totally implantable devices for drug infusion are becoming available, are replacing the bulky infusion machine and may be better-tolerated than external pumps.⁷⁸

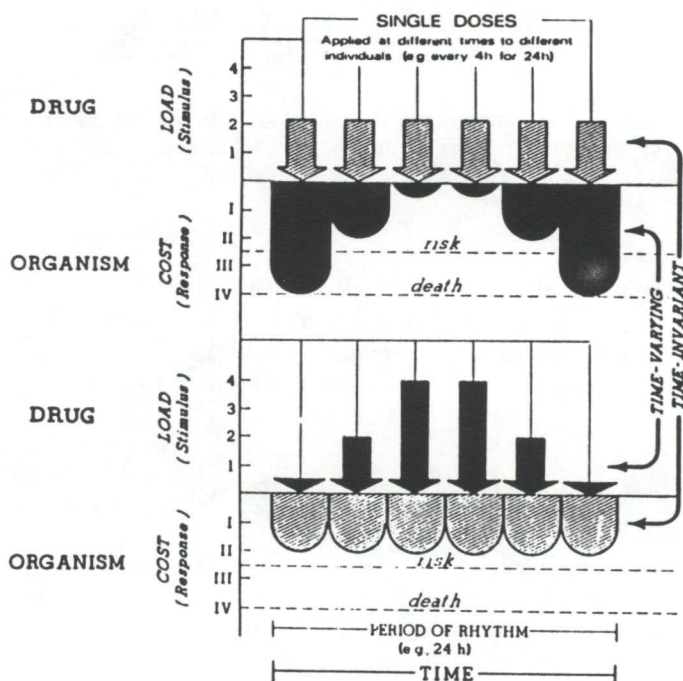
The question then arises from the viewpoint of chronobiology whether drug administration should be continuous or patterned. Continuous administration does not result in constant blood concentrations, since drug metabolism, interactions, and excretion are all periodic.^{34,36,59} Rather than aiming at drug concentrations that relate only to the aforementioned factors, a rational approach can be used, derived from studies on experimental animals.

One method for testing anticancer treatments in the laboratory

is to administer a drug every three hours over a 24-hour span in order to bathe the body frequently if not continually with the anti-cancer substance, and thus to catch any cancer cells that might enter a certain drug-sensitive stage of their cell division cycles. The drug then has the best chance to inhibit or kill the cancer cell. Unfortunately, healthy tissue is also destroyed by the drug. This results in undesired, life-threatening damage, e.g., to the bone marrow, along with the desired reduction in number of cancer cells. The abstract Figures 1 and 2 portray the available evidence and

Rationale for Chronotherapy

Rhythm Determines Cost of Single Drug Administration*



*To minimize side effects of therapy we can systematically vary Timing (above) as well as Dose (below)

Figure 1: Abstract schemes representing a wealth of information on the importance of rhythm stage in the outcome of a desired or undesired response, including death. © 1973 by Halberg.^{8,55}

POTENTIAL BENEFITS OF CHRONOTHERAPY

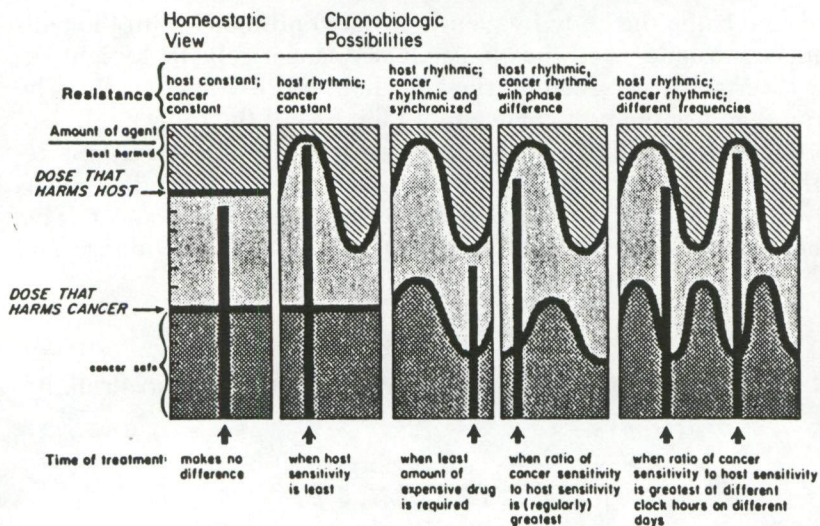


Figure 2: Further abstract summaries of decades of work from many laboratories documenting the rational basis of cancer chronotherapy. © 1973 by Halberg.^{8,55}

rationale underlying chronotherapy in general. It is well known for many agents, including drugs, that a given dose of a potentially harmful agent can be tolerated better at one time than at another time. It seems reasonable, therefore, to vary dosing with timing (Fig. 3).

Chronotherapy via the Drug Pump

An implantable and externally programmable pump such as that in Figures 4 through 8 was used on 21 outbred beagle dogs to administer cyclosporine with one of several circadian sinusoidal schedules or at a constant rate. The dogs were kept in 12 h of light alternating with 12 h of darkness. This experiment is described in part in Figure 9.³⁴⁻³⁶ Untreated dogs only live for 5 to 7 days (not shown). This average of about six days can be improved by treatment with cyclosporine, as shown in Figure 9. Four animals suffice to document the point of a statistically significant improvement

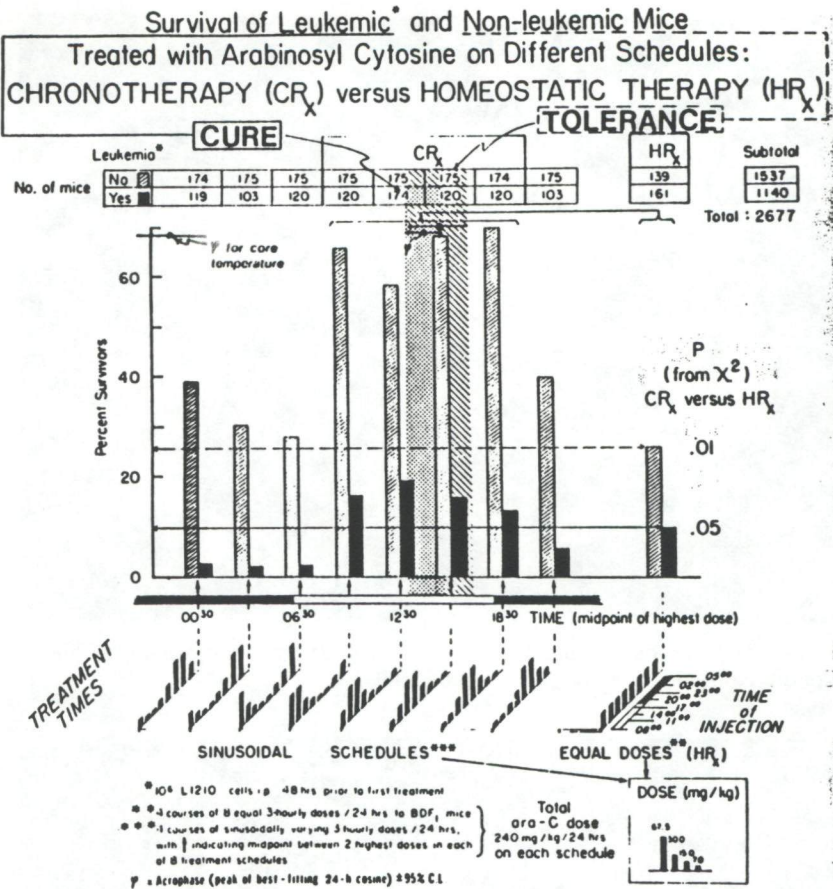


Figure 3: Homeostatic (equal-dose) versus chronobiologic (sinusoidal) treatment of leukemia. The stage of circadian rhythms at the time of exposure to a fixed dose of a potentially noxious stimulus (including antimitotic agents) dramatically tips the scale between death and survival. Such observations were made under standardized conditions, including continuous darkness, to document that rhythms were not simply a function of the lighting regimen or of the time of day. On the basis of such results, a chronotherapy of cancer was considered promising. Several chronobiologists met with a group from the National Cancer Institute (USA) early in the 1970s to draw up acceptable rules for testing the effectiveness of chronotherapy on laboratory animals. It was decided to compare survival times following the administration of an anticancer drug, ara-C, given in four courses of homeostatic (fixed-dose) versus chronobiologic (sinusoidally-varying dose) schedules. This study demonstrated that chronotherapy with ara-C as compared to conventional therapy was less toxic when tested on intact mice and was superior in prolonging the survival time of leukemic mice.⁵⁵ This figure summarizes an early study on both tolerance and cure rate. © 1973 by Halberg.⁵⁵

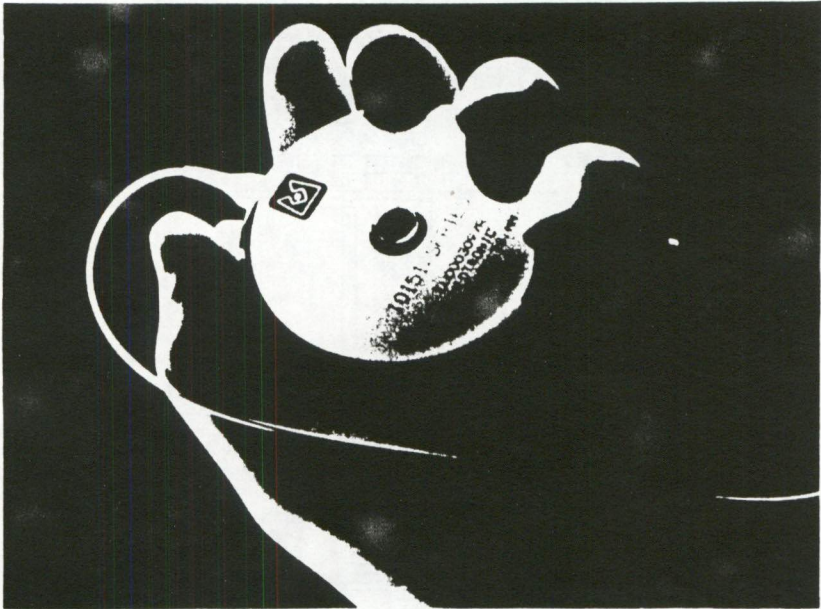


Figure 4: Hand-held implantable externally programmable Medtronic pump. Courtesy of Medtronic Inc., Minneapolis, MN.

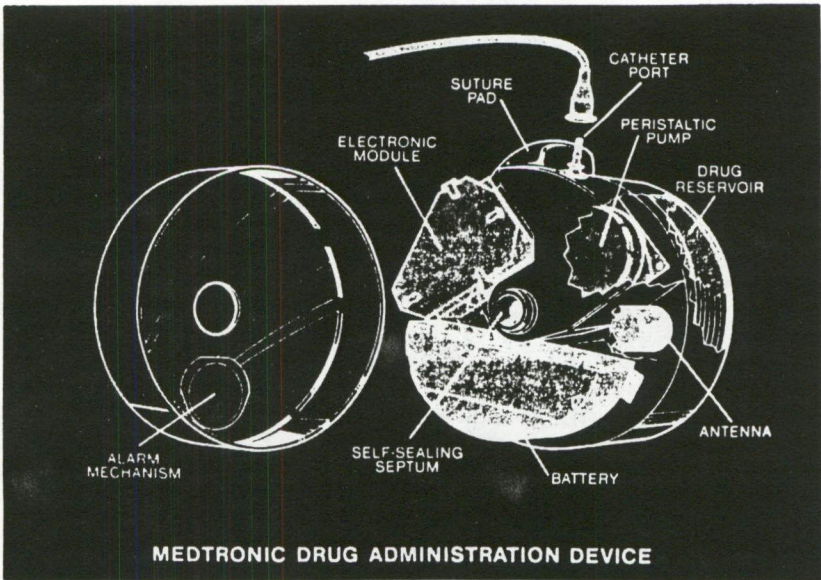


Figure 5: Exploded internal view of an implantable drug administration pump.

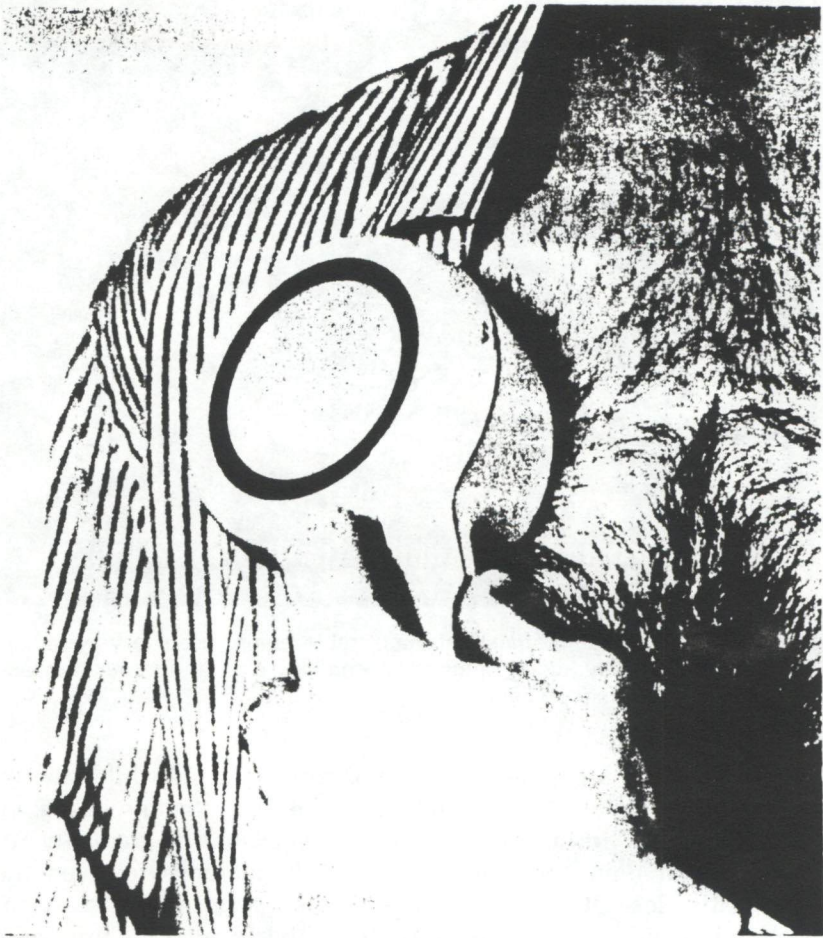


Figure 6: Illustrative programmer WAND location for telemetry link to an implanted pump.

from cyclosporine given by continuous infusion, as compared to the nine untreated dogs ($P < 0.01$).³⁶ This improvement is kept to a modest prolongation so as not to unduly prolong the suffering of the animals and the cost. Against these two reference standards (one from untreated dogs, the other from dogs treated with cyclosporine infused at a constant rate), the results obtained with the sinusoidal schedules given via the drug pump can be compared. With the pump and programmer described in Figures 4 through 7,

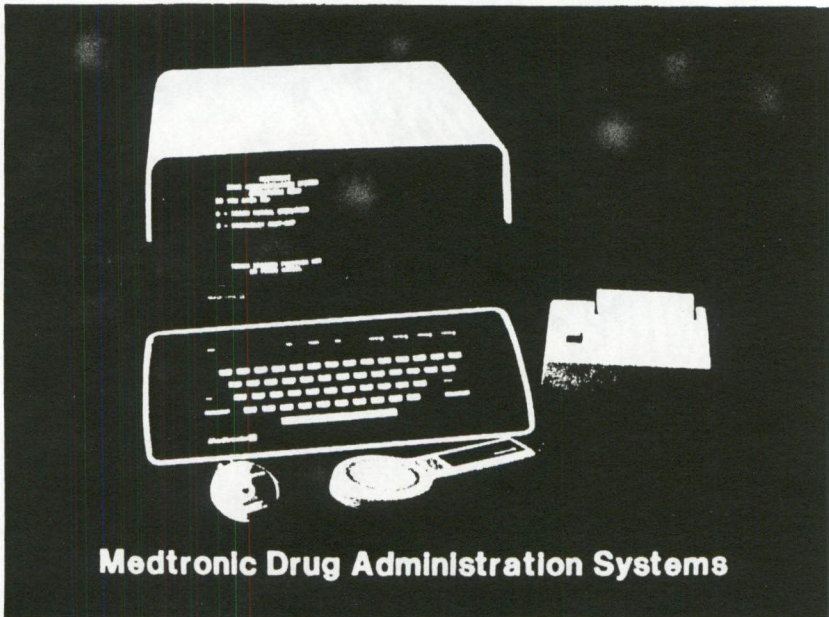


Figure 7: External programmer of implantable pump, used to vary rate of cyclosporine (or any other) infusion according, e.g., to circadian quasi-sinusoidal schedules (see Figure 14).

one can indeed implement the several sinusoidal schedules shown in the bottom half of Figure 9 (cf. also complex schedule in Fig. 8). The sinusoidal timing of cyclosporine consisted of gradually increasing and then decreasing doses. Different dogs received the peak daily dose at a preselected circadian stage. Daily treatment with a sinusoid peaking at the right time, shortly after the middle of the daily dark span, greatly increased the effect obtained as compared to the effect of the same daily dose injected at a constant rate or injected with the sinusoidal schedule peaking at the wrong time (during the light span in the laboratory).

Figure 10 introduces the results from the application cosinor of the method of data analysis^{8,41,42} by showing the 24-h cosine curve best fitting the data obtained with different sinusoidal schedules (shown in Fig. 9). With the fit shown in Figure 10, one can test whether the amplitude of the fitted cosine curve is likely to be zero. In rejecting the zero-amplitude assumption (result not shown), the rhythm can indeed be validated, as is the case for the results on

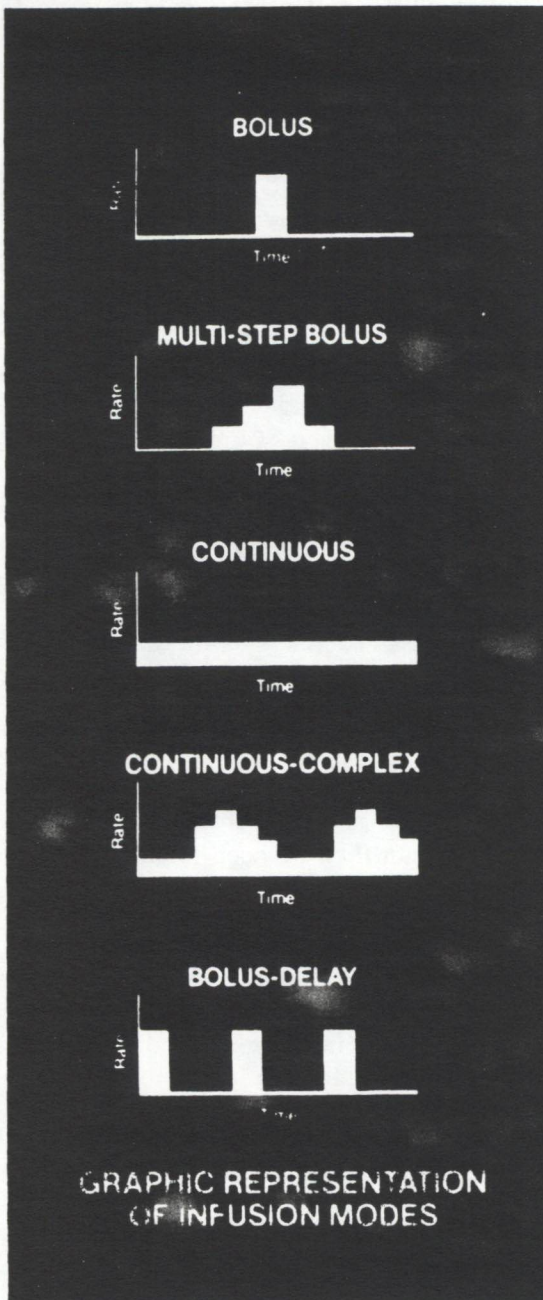


Figure 8: Comparison of various modes of operation of an implantable pump. The continuous complex mode is not complex enough if it is to accommodate at least circadian and circaseptan intermodulations (see text).

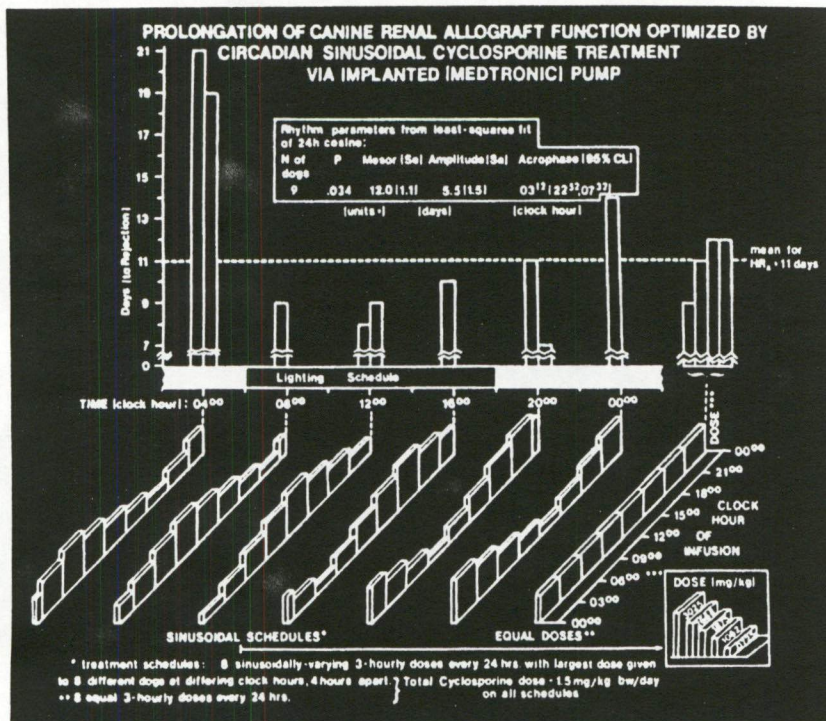


Figure 9: Treatment with sinusoidally varying doses, with different time location of high and low doses, has different effects. Studies by Cavallini et al.³⁴⁻³⁶

cyclosporine in this figure. One can then proceed to an estimation of rhythm characteristics, also shown in Figure 10; it can be seen that the amplitude is of 5.23 days. This amplitude is one-half of the total predictable change due to the organism's rhythmic response, i.e., the extent of change that can be exploited by drug timing. The double amplitude or the total predictable change (not the range of overall variability) is 10 days. The best treatment time derived from these results is also given by the acrophase, an indication of the lag from some arbitrary zero-time (in this case midnight) of the peak in the curve best-approximating all data. It does appear that this best time is 2h, 24 min. after the time reference (i.e., after midnight).

Figure 11 shows the results already shown in Figures 9 and 10 in a different way, namely along polar coordinates, as a step toward the estimation of the uncertainty of the joint rhythm characteristics.

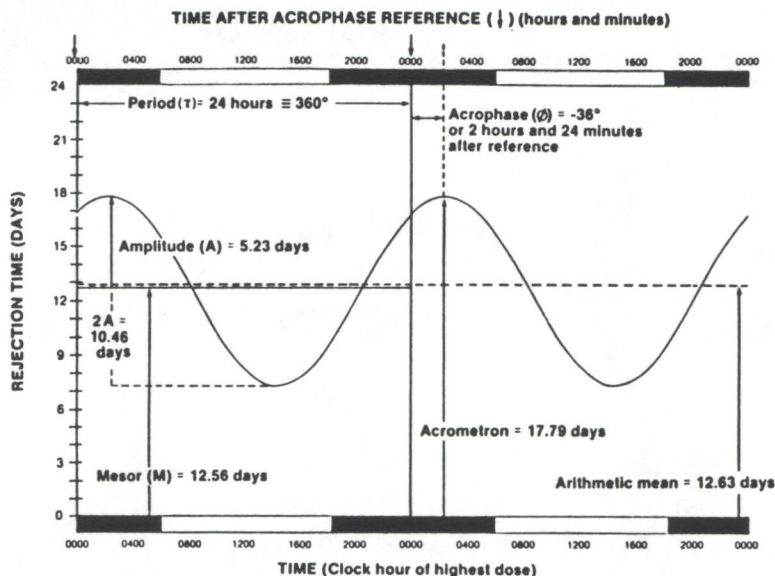


Figure 10: A presentation of rhythm parameters, estimated by the 24-h cosine curve fit, approximates the extent of gain or loss with timing. Studies by Cavallini et al.³⁴⁻³⁶

These characteristics are displayed on a clockface. Midnight is shown on top, noon at the bottom, and 6 a.m. and 6 p.m. are shown on the sides. Negative degrees are shown in a clockwise fashion so that midnight corresponds to 0°, 0600 to -90°, noon to -180°; other times are readily computed if it is realized that 360° are equated to 24 hours, 15° to 1 hour and hence 1° to 4 minutes. A confidence region for the uncertainty of the best time for highest concentrations of the sinusoidal cyclosporine schedule is also represented, in Figure 12, as the elliptical region around the tip of the vector representing the amplitude-acrophase pair.

Once the cyclosporine sinusoid peaking at night was known to be associated with best results, whereas a sinusoid peaking around noon yielded the worst results, two different treatment times were used for follow-up work with oral doses aimed to check on the degree of generality of the result. These were so chosen that one led to blood concentrations that peaked at the anticipated best circadian stage (around 0230); the second peaked about 12 hours later, at the anticipated worst circadian stage. By the choice of these oral

CIRCADIAN OPTIMIZATION OF PROLONGATION BY CYCLOSPORINE OF CANINE KIDNEY ALLOGRAFT FUNCTION

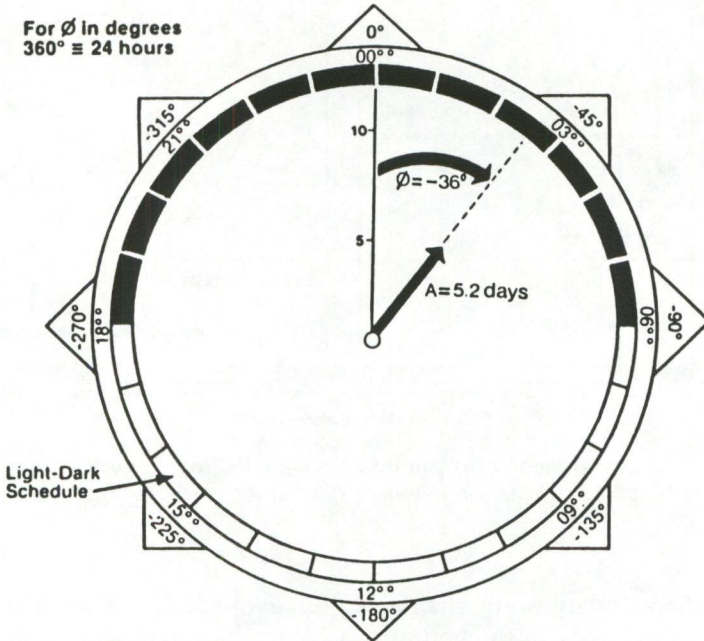
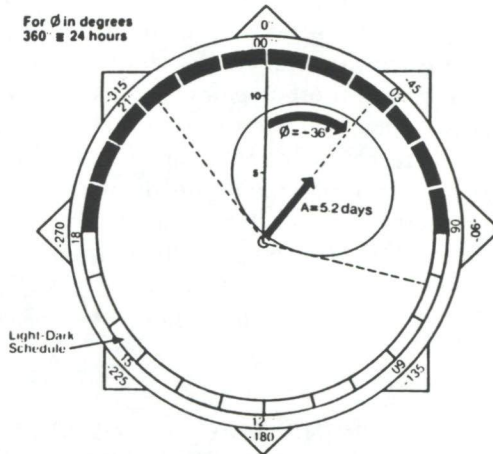


Figure 11: Rhythm parameters are given in polar plot as length and angle of a vector. Studies by Cavallini et al.³⁴⁻³⁶

treatment times, allowance was made for differences in route of administration, for reproducing the time courses of the desired and the undesired cyclosporine concentrations in blood. Pharmacokinetic studies indicated that the intended timing of changing blood concentrations was indeed achieved.^{34,36}

This follow-up study on kidney-allografted dogs validated, with the oral administration of cyclosporine, the results obtained earlier by the use of the pump. As a start, 10 dogs were paired; each had one kidney removed and discarded, while the other kidney was removed and transplanted into its partner in the pair. Within each pair, one dog was assigned to one treatment time while the other

CIRCADIAN OPTIMIZATION OF PROLONGATION BY CYCLOSPORINE OF CANINE KIDNEY ALLOGRAFT FUNCTION



P	No. Obs	PR	Mesor SE (Days to Rejection)	Amplitude(A) (Days to Rejection)	Acrophase(ϕ) (95% C.L.)
0.041	8	72	12.6 1.1	5.2 (3.10.2)	-36° (-321, -108)

P = Probability of hypothesis: Amplitude = 0; No. obs. = Number of observations
PR = Percent Rhythm (percentage of variability accounted for by cosine curve)
95% C.L. = Conservative 95% confidence limits derived from cosinor ellipse

Figure 12: Uncertainty of parameters is shown by 95% confidence region. Studies by Cavallini et al.³⁴⁻³⁶

was assigned to the other treatment time. In an attempt to delay, if not prevent, the transplanted kidney from being rejected, cyclosporine was given orally once each day for as long as the kidney functioned. One dog in each pair received the drug at 0830 every day, while the second dog received the drug at 2030.

Treatment notwithstanding, all dogs receiving cyclosporine in the morning had rejected their grafted kidney by 10 days after surgery. Rejections in this group started as early as 6 days after surgery and were roughly comparable to those of the earlier series. Of the five dogs treated in the evening, the predicted right time, only one dog had rejected the transplanted kidney at 15 days after surgery. Even in this case, there is a 50% increase over the longest graft survival time for dogs receiving the drug in the same dose in the

morning (at the wrong treatment time). The grafts in the other four dogs treated in the evening (at the right time) were still functioning at the time of the first summary. One of these dogs had lived for more than a month after surgery, while its partner, treated at the wrong time, had rejected within one week after surgery. These statistically highly significant results on the first five pairs were confirmed by follow-up work on other pairs of dogs (Fig. 13^{35,36}).

A high-technology product, the drug pump, served in this case as a tool for therapy research leading the way toward a conventional (oral) therapy mode optimized according to circadian rhythms. It has been shown in the interim, however, that much added gain can be derived from a therapy with cyclosporine also optimized according to built-in about-7-day circaseptan rhythms. When multiple circadian and circaseptan patterns, Figure 14, are to be adminis-

TIMING ORAL CYCLOSPORINE single daily dose

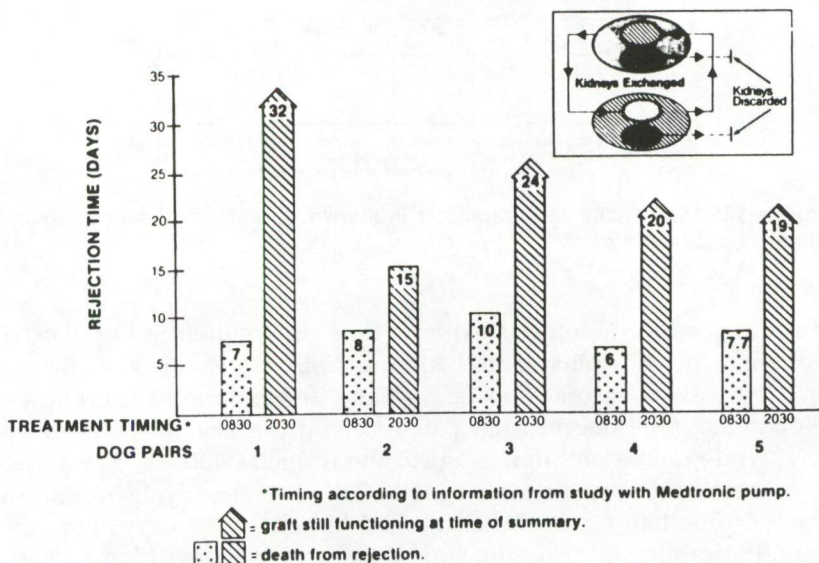
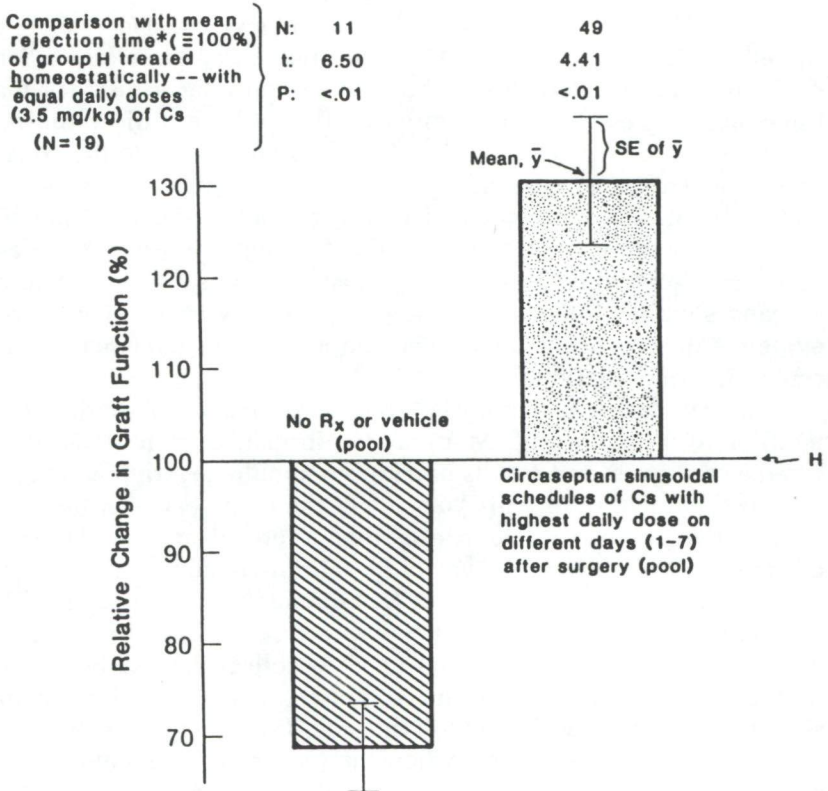


Figure 13: In dogs kept in light from 0600 to 1800, treated either at 0830 or at 2030 with a single daily oral dose of 12.5 mg/kg cyclosporine, the evening dose is over twice as effective as the morning dose in prolonging kidney allograft function. A pharmacokinetic difference is not detected at these particular treatment times. Studies by Cavallini et al.³⁴⁻³⁶

**Circaseptan Optimization of Cyclosporine (Cs)
Transplant-Immunotherapy**
15-27-Week-Old Diabetic Male Ma Lewis (RT-1^L)
Recipient Rats Bearing Segmental Pancreatic Allografts
from Donor ACI Rats (RT-1^a)



*Time to rejection determined by onset-time of hyperglycemia (> 200 mg% lasting ≥ 3 days)

Figure 14: As compared to treatment with equal daily doses, circaseptan dosing schedules (that vary quasi-sinusoidally with a 7-day cycle, irrespective of the timing of the highest dose) prolong graft function.

tered, drug pumps become an indispensable tool. In combination with the use of marker rhythms, they can provide the properly timed "peaks and valleys" in drug concentration, as these are needed for an optimal therapeutic effect (Figs. 13 and 14).

For some of the work with ara-C in Figure 3, a former laboratory staff member, an Olympic runner (he had to be one!), administered the sinusoidal drug patterns. His effort was considerable: he injected 270 mice within 180 minutes; that is, he injected each mouse within less than 60 seconds. At this feverish pace, he continued reinjecting these groups of 270 mice every three hours, for 48 hours. He repeated this 48-hour marathon after a rest day for three more cycles. Even his stamina would not have sufficed for the addition of a second, about-7-day, (circaseptan) pattern to the circadian one. The same demanding patterns, however, are now easily and automatically implemented in the patient by an implantable externally programmable pump. Indeed, more complex schedules than a single set of increasing and decreasing doses during 24 hours can and should be given with the pump in view of the exhaustive evidence documenting the clinical importance of circadian-circaseptan intermodulation.^{35,36}

The next task is to administer drugs according to marker rhythms monitored automatically. Monitored information should be analyzed as one goes, and results of analyses should govern the pattern of drug administration. This "closing of the loop" between the dispenser (the pump) and the sensor (of the organism) constitutes a desirable development. As yet only a limited number of marker rhythms, such as those of the ECG, EEG, blood pressure, respiration, motor activity, and body temperature can be monitored automatically around the clock. The need to collect data manually is now eliminated in these instances, but the need to analyze them automatically remains. Even with this qualification, marker rhythmometry is particularly useful when the period of a patient's pertinent rhythm(s) is different from precisely 24 hours, as can be the case for electrocardiographic abnormality.³⁶ The data from ambulatory monitoring devices have to be properly analyzed to test the possible merits of various applications in fields including, among others, cardiology and immunology as well as cancer. Eventually, there may be pacemaker-pump systems for properly scheduled, i.e., timed electrical and pharmacologic combination treatment. It seems reasonable to suggest, on the basis of available evidence, that all treatment should be timed, in any event.

Another Challenge to Chronobioengineering: A Blood Pressure and Related Cardiovascular Summary, the Sphygmochron*

The range of blood pressure variability in health is as large as (or even larger than) the difference between systolic and diastolic pressure. When analyzed chronobiologically, part of this variability is predictable in that it can be objectively characterized by sensitive parameters of extent (the amplitude) and timing (the acrophase and, in the case of long series, the period) of rhythmic change. Although part of this predictable or rhythmic variability occurs with changes in activity or posture, the circadian blood pressure rhythm persists in recumbency.⁶³

The great variation in blood pressure was recognized before the turn of the century; chronobiologists have long advocated that part of this variability can be rendered predictable by assessing rhythm characteristics. This task can be aided by modern instrumentation for monitoring and analysis. The issue of whether one should rely on manual or automatic blood pressure measurement is being discussed, however, apart from assessing any predictable variability, as a matter of cost-effectiveness. The availability of new instrumentation prompts the question of whether it is worth monitoring around the clock to obtain a more reliable mean rather than a casual pressure. From a chronobiologic viewpoint, a much broader issue is not only how, but also how often and when to measure and whether to interpret data *homeostatically* or *chronobiologically*.⁷⁹

Homeostasis focuses upon the blood pressure, relying on casual measurements such as those recommended in the World Health Organization (WHO) Guidelines. For a test of a mild blood pressure elevation, defined as 90–104 mmHg diastolic, without organ damage and “to provide a safe classification of patients,” the International Society of Hypertension joins WHO in recommending the criterion of the mean of two (casual) diastolic measurements. If the mean of these is 90 mmHg or above, further measurement pairs on at least two further days over four weeks are recommended. If the mean values of these are above 100 mmHg, drug treatment is to start. If in turn these means are below 100 mmHg, further measure-

**Sphygmo*—: of or relating to the circulating pulse, notably blood pressure; *chronos*: time.

ments over three months and behavioral intervention, but not drug treatment, are recommended. If the overall mean is now above 95 mmHg, drug treatment is recommended; if the mean is below 95 mmHg, behavioral intervention is prescribed with further observations over three months. It is left to the individual to pick the time of measurements.

Chronobiology focuses upon both the predictable and the global dynamics of the variation in blood pressure and detects pressure elevations that are likely to be missed if one measures at only one or another convenient time of day. Some treated or untreated cases show elevations during odd hours when measurements, as a rule, are not taken. To detect such cases, systematic manual or preferably automatic around-the-clock measurement is required. With such series available, one takes into account a usually large circadian variation that, under ambulatory conditions in clinically healthy North American men, averages well over 60 mmHg systolic and over 50 mmHg diastolic. Part of this variation is resolved as predictably rhythmic by the fit of cosine functions with periods of 24 hours and submultiples thereof. The characteristics (MESOR, amplitudes and acrophases of the 24-hour and additional harmonics—10 of them if the data are densely obtained from automatic measurements) constitute a section of blood pressure-related cardiovascular summaries, the so-called sphygmochrons, shown as a short form (S), Figures 15 and 16, or long form (L), Figure 17, respectively. On the face of the form, peer group reference limits for rhythm characteristics are given for the fit of a 24-hour (form-S) or for that of both a 24- and 12-hour (form-L) cosine curve. The key is on the back of the short form, Figure 17, and in the upper right-hand corner of the long form. On the back of the form, one can add results related to further harmonics and to comparisons of single or multiple rhythm parameters with so-called parademes, one kind of chronodesm, and displays for the interpretation of time-specified single values in the light of time-specified 90% prediction limits—other chronodesms. Chronodesms are best based on data for a peer-group with the same ethnicity, age, and gender. Chronodesms vary with the conditions of measurement, e.g., as a function of whether the subject is ambulatory, room-restricted, sitting, or recumbent. For each case, the chronobiologic approach has to provide a separate set of reference intervals (and eventually should provide conversion factors) for single blood pressures that are time-specified; for the characteristics of the fundamental and additional harmonics (whereby the

SPHYGMOCHRON™**BLOOD PRESSURE (BP) AND RELATED CARDIOVASCULAR SUMMARY.**

(Circadian Sphygmochron, from sphygmo-, of or relating to the circulating pulse, notably blood pressure, and chrono-, time)

**COMPUTER COMPARISON
MONITORING PROFILE OVERTIME
PROJECTED AGAINST
PEER GROUP
LIMITS**

Name _____ Patient # _____ No. of Profiles: _____

Age _____ Sex ☐ M ☐ F Monitoring From _____ To _____, 19 _____**TIMES OF**Awakening: Day of Profile
Habitually _____

Activity? _____

Breakfast _____
Diet? _____Going to Sleep: Day of Profile
Habitually _____Shift Schedule: Yes ☐ _____

Lunch _____

Drugs? _____

If Yes, Explain: _____

Dinner _____

Snack _____

CHRONOBIOLGIC CHARACTERISTICS

	SYSTOLIC BP (mmHg)		DIASTOLIC BP (mmHg)		HEART RATE (bpm)	
	PATIENT VALUE	PEER GROUP REFERENCE LIMITS	PATIENT VALUE	PEER GROUP REFERENCE LIMITS	PATIENT VALUE	PEER GROUP REFERENCE LIMITS
ADJUSTED 24-h MEAN (MESOR)		 RANGE		 RANGE		 RANGE
PREDICTABLE CHANGE (DOUBLE AMPLITUDE)		 RANGE		 RANGE		 RANGE
TIMING OF OVERALL HIGH VALUES (ACROPHASE)		 RANGE		 RANGE		 RANGE

PERCENT TIME OF ELEVATION			
EXTENT OF EXCESS	(mmHg x hour)	(mmHg x hour)	(bpm x hour)
10 YEAR CUMULATIVE EXCESS	(mmHg x hour) (in 100,000's units)	(mmHg x hour) (in 100,000's units)	(bpm x hour)
TIMING OF EXCESS			

INTERVENTION NEEDED

- ☐ No
☐ Yes ☐ Drug ☐ Non-Drug

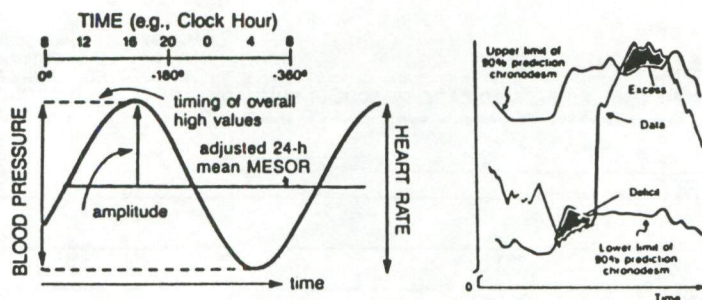
MORE MONITORING NEEDED

- ☐ Annually
☐ As soon as possible
☐ Other specify _____

PREPARED BY _____ DATE ____/____/____

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Figure 15: Front of sphygmochron-S, the short form of a blood pressure and related cardiovascular summary.



MESOR, (M) rhythm-adjusted mean (midline-estimating statistic of rhythm), defined as average value of rhythmic function (e.g., cosine curve) fitted to data; expressed in same units as original data. Note that MESOR will differ from arithmetic mean if data are unequidistant (e.g., concentrated near crest of rhythm) and/or cover non-integral number of cycles.

AMPLITUDE, (A) half of total predictable change in rhythm, defined by rhythmic function fitted to data; expressed in original or "relative" units, e.g., as percentage of series mean or MESOR.

ACROPHASE, (ϕ) lag from reference time of rhythm's crest-time, defined by rhythmic function fitted to data; usually expressed in (negative) degrees, with 360° = period, 0° = reference time; customary time units (e.g., clock-hours and minutes, days, weeks, months or years); physiologic units (e.g., number of heart beats, respiratory or menstrual cycles) also appropriate for rhythm synchronized with corresponding period.

Figure 16: Back of sphygmochron-S, the short form of a blood pressure and related cardiovascular summary.

waveform is also accounted for); and in addition, for excess or deficit assessed on the basis of a data set as a whole, compared to the appropriate (earlier-determined) individualized and/or peer-group chronodesms. Automated measurements are superior to self-measurements at the outset, until a personal set of reference values is established, with both automatic and manual self-measurement under real-life conditions. As a complement, monitoring under standardized conditions is also desirable, to assess both the spontaneous and reactive blood pressure dynamics.

The use of the sphygmochron starts with newborn monitoring. The conventional approach does not work, in that a mean or a standard deviation of extensive series (such as half-hourly measurements for 48 hours) does not separate groups of newborns with a positive versus negative family history of high blood pressure, Figure 18. As Figures 19 and 20 show, however, the chronobiologic approach does so by the criterion of a circadian amplitude.³⁷ The difference in linear trend during the first two days of life is not shown in the normalized data of Figure 19 and their analysis in Figure 20. The trend is unmasked in part as the onset of the about-

BLOOD PRESSURE AND RELATED CARDIO-VASCULAR MONITORING SUMMARY OVER TIME*

(Circadian Sphygmochron; from sphygmogram, or of relating to the circulating pulse, notably blood pressure, and chronos, time)

Name _____

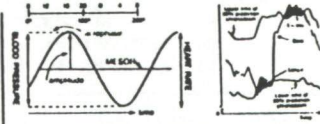
Age _____ Sex ☐ M ☐ F From _____ To _____, 19____

TIMES OF

Awakening _____ Activity? _____ Diet? _____

Drugs? _____

Going to Sleep _____



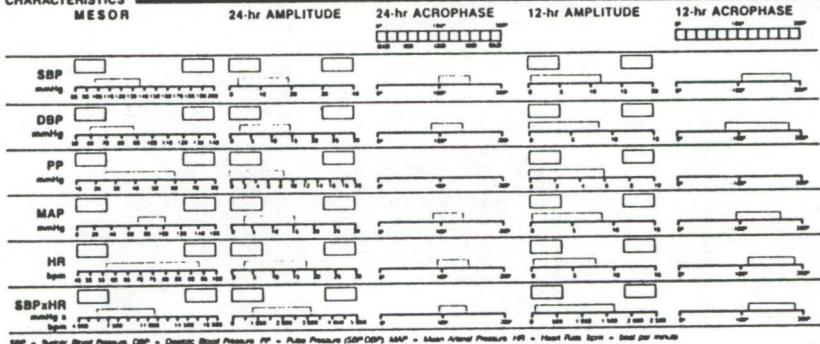
MESOR, (24) rhythm adjusted mean (adjusted) sinusoidal profile of rhythm, defined as average value of rhythmic function by π (period) divided by 2π , expressed in same units as original data. Note that MESOR will differ from arithmetic mean if data are unisynchronous (e.g., concentrated near crest of rhythm under cover non-rigid number of cycles).

AMPLITUDE, (24) half of total predictable change in rhythm, defined by rhythmic function based to data expressed in original or "reference" units, e.g., as percentage of some mean or MESOR.

ACROPHASE, (24) long term reference time of rhythm's crest time, defined by rhythmic function to data in data, usually expressed in fractional degrees, with 360° = period, 0° = reference time.

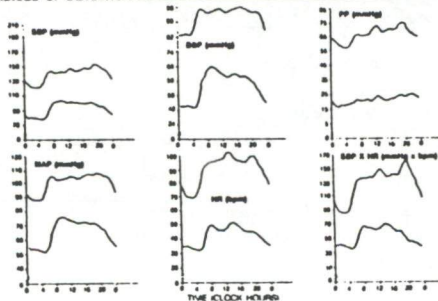
Units: (e.g., number of heart beats, respiratory or muscular cycles) also appropriate for rhythmic syn-chronized with corresponding period.

CHARACTERISTICS¹



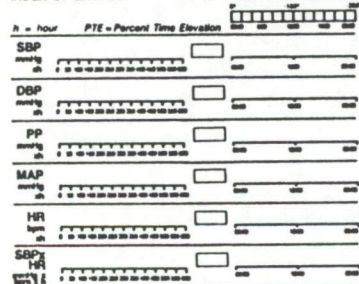
SBP = Systolic Blood Pressure DBP = Diastolic Blood Pressure PP = Pulse Pressure (SBP-DBP) MAP = Mean Arterial Pressure HR = Heart Rate bpm = beats per minute

INDICES OF DEVIATION



INDEX OF EXCESS^{2,3}

PTE TIMING OF EXCESS



INTERVENTION NEEDED

YES ☐ NO ☐

PREPARED BY _____ DATE (YR, MO, DAY) _____

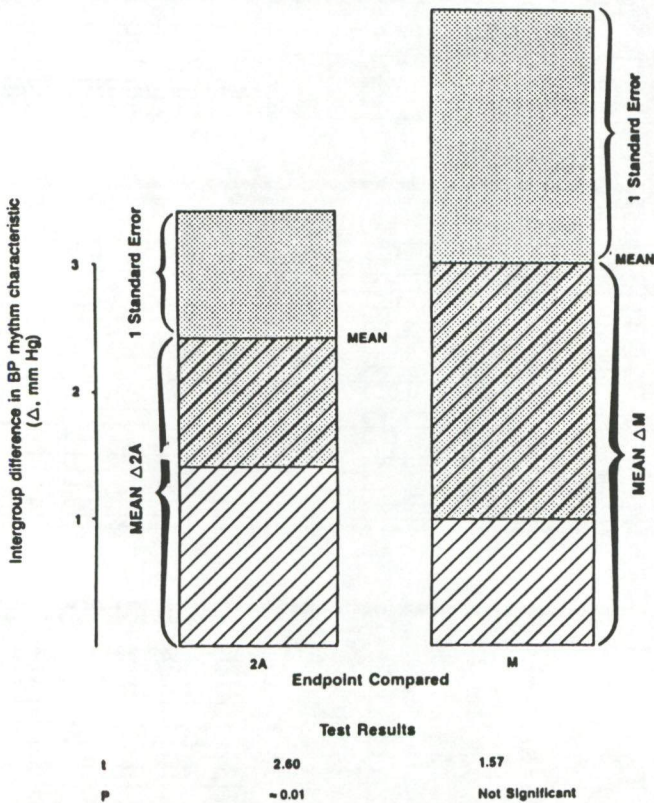
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1) Unusually long standing or lying-down during waking, unusual activity, such as exercise, etc. 2) Salt, calories, other, etc. 3) Kind and amount, if any. 4) Rectangles on baseline indicate acceptable ranges, other rectangles serve for values off scale. 5) Values calculated with respect to 7) Chronometric limits (time-spread) (80% probability limits) or with respect to 7) blood limits, determined on the basis of the median acrophase (MESOR) amplitude, i.e., highest predictable value of a peer group. Check the box (1) if index of excess rather than excess.

* Crosses on form indicate results from your individualized cardiovascular monitoring profile. If numbers (instead of crosses) are used, they refer to several issues of your monitoring, along with results of tests for any changes in circadian parameters. (See comments on reverse side, that may also refer to rhythms other than circadian under trends.)

Figure 17: Sphygmochron-L, long form of a blood pressure and related cardiovascular summary.

Double circadian amplitude (2A, left) but not the MESOR (M, right) separates groups of newborns with a positive versus a negative family history of high blood pressure (BP), while numerically the difference (Δ) in 2A (left) is smaller than that in M (right).*



* The smaller standard error of the $\Delta 2A$, as compared to that of ΔM , accounts for the better resolution of $\Delta 2A$.

Figure 18.

7-day rhythm shown in Figure 21; again, one finds that the chronobiologic approach, i.e., the circaseptan amplitude, just as does the circadian one, distinguishes the groups with a positive versus negative family history of high blood pressure, when the mean value does not work (Fig. 18).

Data collection and summary by sphygmochron should start at

A great challenge lies in recognizing cardiovascular risk at birth on the basis of the precocious development of the circadian and circaseptan blood pressure (BP) amplitudes. In ongoing research, the newborn's BP and heart rate are being monitored automatically for 48 hours. The data are analyzed chronobiologically. Whether the index can be changed by preventive measures instituted on the pregnant woman acting *in utero* alone is a topic for research. The results thus far show a circadian variation apparent to the naked eye in neonates with a family history of high blood pressure (right) but not in those without such a family history (left). In the preparation of this display, the original data of each series are first expressed as percent of their series mean. Thereafter, they are stacked for consecutive hours of an idealized day and averaged.

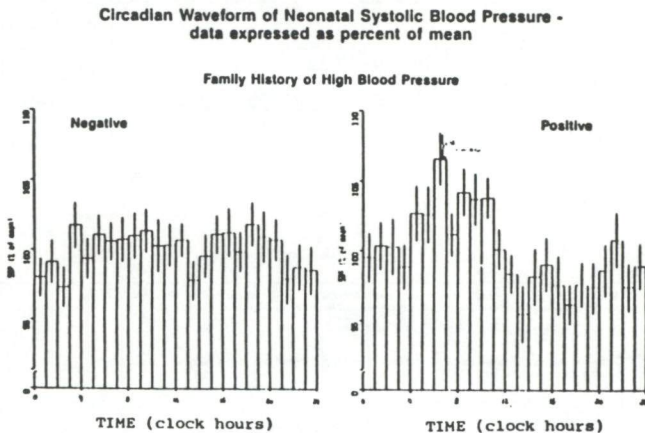
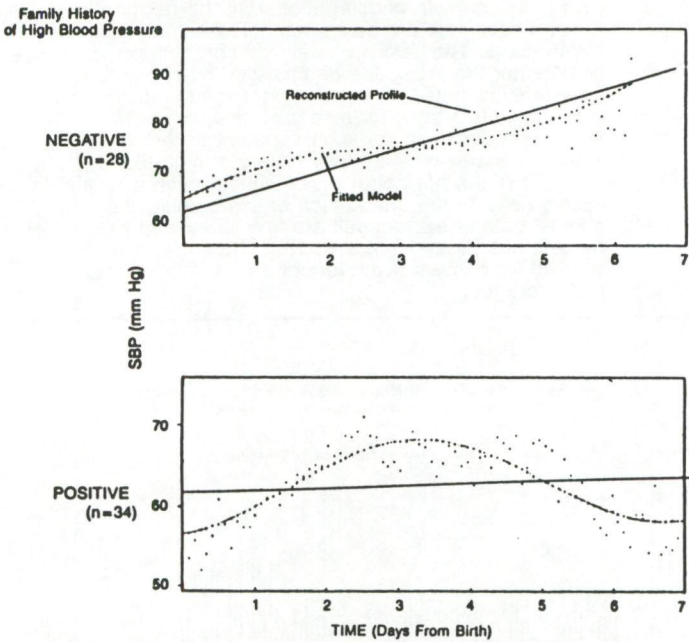


Figure 19.

birth and continue in family and school. Primary and again secondary schooling can serve for the teaching of instrumentation use, data self-analysis, and self-interpretation. For this purpose, the engineering community again faces the task of developing an autochronor in which self-measurements or simple automatic measurements are introduced and analyzed by chronobiometry.⁶⁵ Once chronobiologic literacy wedded to computer literacy becomes obligatory, the criteria of the sphygmochron lead not only to an early detection of overt disease, but also to a recognition of risk elevation. Thus, non-drug treatment can be recommended, before blood pressures exceed

A linear increase and a circaseptan feature characterize systolic blood pressure (SBP) of newborns observed during the first week of life.*



*Weekly profile reconstructed from a data pool contributed by newborns starting 48 h monitoring (at 30-min intervals) at different times after birth. Model listed to reconstructed profile:

$$Y(t) = a_0 + a_1 t + A \cos \left(\frac{2\pi t}{168} + \phi \right) + e(t)$$

Circadian aspect handled separately in Section XI, is ignored for these reconstructions of circaseptan structure.

Figure 20.

currently recommended limits. This is warranted in view of insurance company statistics. These already reveal, with pressures for men and women starting at 118 and 114 mmHg systolic and 72 and 71 mmHg diastolic, respectively, an increase in blood pressure-related morbidity and early mortality as the value of blood pressure increases.⁸⁰

At even lower pressures, it is possible to distinguish, with chronobiologic methods, those found (by epidemiologic questionnaire) to be at a high versus low risk of developing a high blood

The many displays of the chronobiologist need not remain a matter of research. As illustrated earlier, these so-called cosinor methods describe the rhythm by a vector. The length of this directed line corresponds to the extent of change, the amplitude. The orientation of the vector shows the timing of high values. The uncertainty of the summary is also given, as a confidence region around the vector's tip. On the left is the cosinor summary for blood pressures (BP) from a group of neonates with a negative family history of high BP; the confidence region of the vector covers the center of the display. By contrast, for the group of neonates with a positive family history of high BP on the right, the cosinor plot shows that a rhythm is found, as seen from the fact that the confidence region of the vector does not cover the center of the plot and thus the zero-amplitude (i.e., the no circadian rhythm) hypothesis, is rejected.

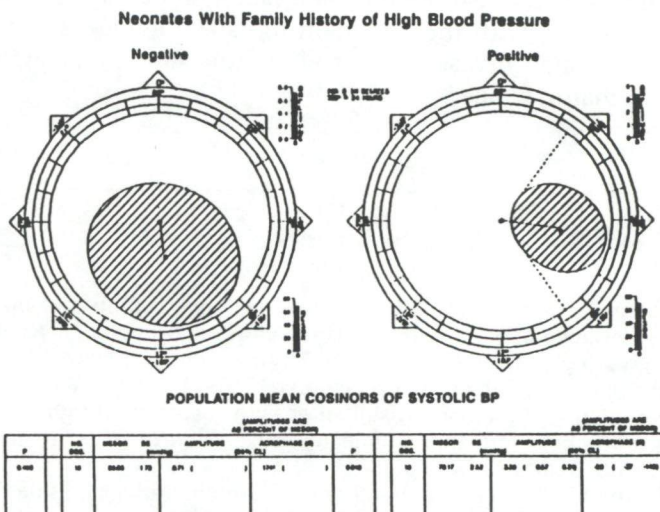


Figure 21.

pressure later in life. Thus, measurements at 10-minute intervals for 24 hours in recumbency on women in high versus low-risk groups reveal a circannual mean, in mmHg, of 108 versus 100 systolic and 69 versus 64 diastolic, respectively.¹⁰ Chronobiologically, novel characteristics of genetic and reactive components of time structure, are quantified in human blood pressure for preventive as

well as curative intervention. At the bottom of each sphygmochron, any such need is also indicated on the basis of statistical inference applied to the individual.

Epilogue

The detailed references indicating the scope of chronobiology should stimulate those in the fields of health and engineering to join forces so that progress is made far beyond the illustrative examples chosen herein. If rhythms are the dynamics of all life, the scope of bioengineering may well be to assess rhythm alterations that are harbingers of earliest risk elevation. The harbingers, in turn, should prompt preventive intervention before elevated risk turns into overt disease. Rather than being concerned primarily or even exclusively with the treatment of catastrophic disease, as we are now, we may invest a major effort into chronobioengineering for health maintenance.

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Addendum

Since this paper was prepared, two added references can be listed (both of which may be obtained by request from Patrick Delmore, Head, Corporate Communications, Medtronic Inc., 7000 Central Ave. N.E., Minneapolis, MN55432, USA):

Halberg F., Delmore P., Bakken E., Cornélissen G., Shinoda M., Tarquini B., Scarpelli P.T., Sánchez de la Peña S., Wu J., Halberg J., Halberg E., Germanó G., Cagnoni M.; Chronobiologic blood pressure and heart rate assessment in clinical practice: today and tomorrow.

Halberg F., Cornélissen G., Halberg E., Halberg J., Delmore P., Shinoda M., Bakken E.: Chronobiology of human blood pressure. Medtronic Continuing Medical Education Seminars, 1987, 2nd ed., 234 pp.

From Various Kinds of Heart Rate Variability to Chronocardiology

Germaine Cornélissen, PhD, Dr.h.c., Dr.h.c. Earl Bakken, Patrick Delmore, BFA, Kristina Orth-Gomér, MD, Torbjörn Åkerstedt, MD, Orazio Carandente, MD, Franca Carandente, MD, and Franz Halberg, MD

We wish to show that cardiologic variability can be examined with benefit by the concepts and computer methods of chronobiology, the science (logos) of life's (bios) time (chronos) structure. From heart rate data in a recent article,¹ dynamic end points are obtained to quantify health.² On a group basis, when conventional end points applied to 2 sets of electrocardiographic records fail to separate for sudden adult death, chronobiologic end points already do so.² Novel information not obtained by conventional location or dispersion indexes³ can be provided by the computation of the circadian and other amplitudes.⁴ Beyond sudden death after myocardial infarction, the importance of these amplitudes has been demonstrated in several additional cases of cardiologic interest²: (1) the amplitudes of several rhythmic components of systolic or diastolic blood pressure separate groups of human newborns with a positive versus negative family history of high blood pressure or cardiovascular diseases, or both, when the mean based on the same data does not do so; (2) in children ≥ 9 years old, the circadian amplitude and acrophase of blood pressure, but not the mean, separate groups at low or high risk of developing high blood pressure later in life; (3) at 15 years of age, the circadian amplitude of diastolic blood pressure, but not the mean, correlates with the thickness of the interventricular septum of the heart.

Rhythm indexes that serve on a group basis as classifiers and potential harbingers of a heightened cardiovascular risk will have to be individualized for use in the clinic as well as in research. The task on hand is to assess the relative merits of the various uses of time-unqualified model-free end points^{5,6} when they work versus the use of chronobiologic indexes, such as the rhythm characteristics of the acceptable (in this sense "normal") heart rate. In this context, a single 24-hour cycle from a circadian viewpoint corresponds to the radial pulse based on a single heartbeat. Chronobiologic recorders and analyzers that store and analyze the data as one goes, already available in chronobiologic pacemaker prototypes, may constitute a step in the direction of obtaining sufficient data for preventive rather than "after-the-fact" therapy.

When viewed on original records, circadian changes can be very irregular. This irregularity can be smoothed by averaging. Circadian changes in heart rate and blood pressure can then be displayed in time plots, time-macroscopically.¹⁻³ Statistical location indexes, such as hourly means over 24 hours, can be used to illustrate the changes in the variables themselves and also in the variability of a given body function, estimated as a dispersion index, such as the standard deviation or the standard error of measurements collected over consecutive hourly spans. Graphs of both hourly means and standard errors along the scale of 24 hours have been published for subjects with a seemingly acceptable or elevated blood pressure³ and analyzed⁴ by the fit of a 24-hour cosine curve and harmonics performed with the precautions of the time-microscopic technique of the cosinor.² Rhythms, in a strict sense, can be defined as algorithmically formulated recurrent changes validated by inferential statistical means. Recently, differences in the circadian timing of changes in heart rate and its variability were reported in the light of paired *t* tests and coefficients of variation applied to electrocardiographic records of 22 healthy vol-

From the Chronobiology Laboratories, University of Minnesota, 420 Washington Avenue, SE, Minneapolis, Minnesota 55455, Medtronic Inc., 7000 Central Avenue, NE, Minneapolis, Minnesota 55432, Karolinska Institute, Stockholm, Sweden, and the University of Milan, Milan, Italy. This study was supported in part by Grant GM-13981 from the U.S. Public Health Service and Grant HL-40650 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and by the Dr.h.c. Dr.h.c. Earl Bakken Fund and the Dr. Betty Sullivan Fund, Minneapolis, Minnesota. Manuscript received March 8, 1990; revised manuscript received May 25, 1990, and accepted May 28.

TABLE I Improvement over 1-Component Model from 2- and 3-Component Models Fitted to Healthy Human Subjects, Heart Rate Mean (HR) and Standard Deviation (SD)

Trial Period (hrs)	PR	Amplitude $\pm$ SE	Acrophase, $\phi \pm$ SE	[Bathypphase]	p Value* Var Hom
HR (beats/min)					
1-component model					
24	83	11.4 $\pm$ 1.1	-249° $\pm$ 6	[-69°]	<0.001
2-component model					
24	83	11.4 $\pm$ 0.7	-249° $\pm$ 4		
12	11	4.1 $\pm$ 0.7	-331° $\pm$ 10		
Overall	94	12.3	-204°	[-24°]	<0.001
3-component model					
24	83	11.4 $\pm$ 0.4	-249° $\pm$ 2		
12	11	4.1 $\pm$ 0.4	-331° $\pm$ 6		
8	4	2.7 $\pm$ 0.4	-68° $\pm$ 9		
Overall	98	13.8	-260°	[-80°]	0.819
SD (RR; ms)					
1-component model					
24	69	11.0 $\pm$ 1.6	-72° $\pm$ 8	[-252°]	<0.001
2-component model					
24	69	11.0 $\pm$ 1.0	-72° $\pm$ 5		
12	20	5.9 $\pm$ 1.0	-168° $\pm$ 10		
Overall	88	13.6	-80°	[-260°]	<0.001
3-component model					
24	69	11.0 $\pm$ 0.6	-72° $\pm$ 3		
12	20	5.9 $\pm$ 0.6	-168° $\pm$ 5		
8	9	3.9 $\pm$ 0.6	-238° $\pm$ 8		
Overall	97	15.0	-80°	[-260°]	0.321

* p values for rejection of zero amplitude assumption are invariably <0.001 for each component in the 3 models fitted (not shown). As to p values from test of assumptions underlying the multiple component model, a p >0.05 validates the fitted model, whereas a p <0.05 provides information concerning data departure from underlying assumptions. The normality of residuals was tested by a Shapiro-Wilk test (p >0.05 in each case, not shown). When a regression diagnostic test yields p values <0.05, transformations or alternate models are to be considered. The addition of a third component, in the case of the data analyzed herein satisfies the test of homogeneity of variance. Goodness of fit tests of the model could not be performed because replicates were not available (a limitation to analyses based only on published data taken off the chart).

Mean and standard deviation of cardiac cycle lengths calculated for 5-minute intervals and averaged hourly over 24 hours. Adapted with permission from Huikuri et al.¹

Acrophase and bathypphase are the lag from midnight of the crest and trough time of the model fitted to the data, respectively, expressed in degrees, with 360° equated to 24 hours.

SE = standard error; var hom = homogeneity of variance.

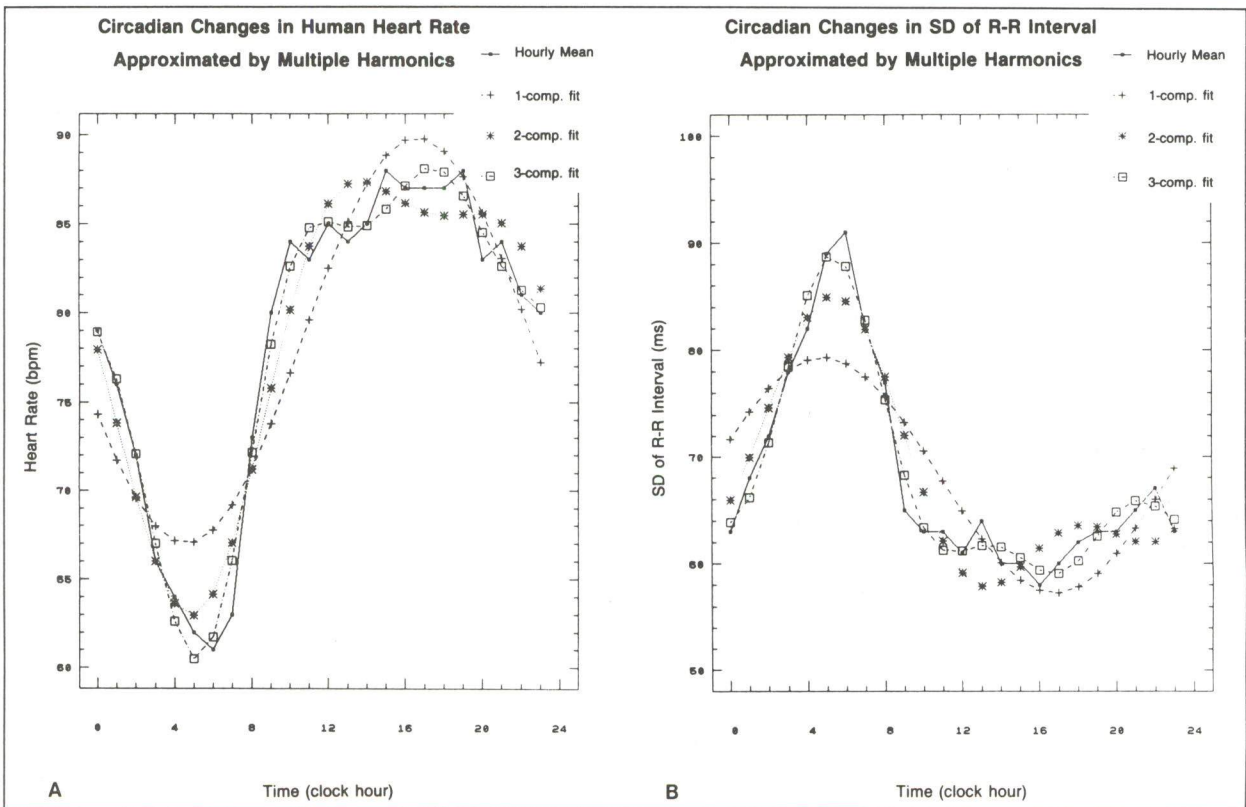


FIGURE 1. Circadian rhythm in (A) heart rate (in beats/min) and in (B) standard deviation of RR intervals (in milliseconds) approximated by a 24-hour cosine curve alone or with 1 (12-hour) or 2 (12- and 8-hour) harmonic components; original data of Huikuri et al.¹ taken off published graph; mean $\pm$ standard deviation of cardiac cycle lengths calculated for 5-minute intervals and averaged hourly over 24 hours.

unteers, each contributing data for 2 or 3 twenty-four-hour spans.¹ Heart rate variability was expressed as the standard deviation of normal cardiac cycle lengths during successive 5-minute intervals, averaged hourly and displayed over the course of 24 hours in parallel with hourly heart rate means.

Cosinor analyses of averages taken off the published graph¹ (Figure 1) validate a circadian rhythm for heart rate and its variability ($p < 0.001$), accounting for 83 or 69% of the total variance, respectively (Table I). These analyses derive rhythm characteristics revealing, when the data are expressed as a percentage of the mean, a difference in timing ($p < 0.001$) in the absence of a difference in amplitude ($p = 0.571$) between the 2 variables. As a measure of timing, the acrophase is expressed in degrees as the lag from midnight (0°) of the crest time in the cosine function fitted to the data ($360^\circ = 24$ hours, $15^\circ = 1$ hour and $1^\circ = 4$ minutes). Whereas the heart rate "peaks" at $-249^\circ \pm 6^\circ$ from midnight ($16:36 \pm 0:24$), the standard deviation of the RR intervals peaks almost in antiphase, at $-72^\circ \pm 8^\circ$ ($04:48 \pm 0:32$) from midnight (Figure 1). The consideration of the second (12-hour) and third (8-hour) harmonics further improves the fit, accounting for 98 and 97% of the total variance without unduly altering the acrophase estimates (Table I). Such end points complement other approaches to heart rate variability.

Kleiger et al⁵ define variability as "... the standard deviation of all normal RR intervals in a 24-hour continuous electrocardiogram recording ...," whereas Rich et al⁶ calculate it as "... 5-minute means of sinus cycle lengths," assessed in 24-hour ambulatory electrocardiograms. The association of an increased mortality after a myocardial infarction with a reduced heart rate variability (standard deviation of RR intervals < 50 ms) reported by Kleiger et al⁵ suggests an association with the circadian amplitude of heart rate. The standard deviation derived from 24-hour recordings may indeed be considered as a rough approximation of the circadian amplitude. This impression is supported by a statistically significant correlation between these 2 indexes for a population of 40 clinically healthy men, 20 to 60 years of age, monitored at 7.5-minute intervals for 24 hours on 2 occasions^{7,8} (data averaged hourly, $r = 0.946$, $p < 0.001$; Figure 2).

It is important to specify how heart rate variability is assessed. A reduced heart rate variability (computed on 5-minute spans) was also found by Rich et al⁶ to correlate with mortality in patients undergoing elective coronary angiography, but not with other clinical, angiographic or Holter variables. When computed over the whole 24-hour span by Kleiger et al,⁵ it did so, although on a different sample. A difference between the 2 approaches to compute heart rate variability may contribute to these results, relating to different (circadian versus ultradian) regions of the spectrum. When computed over hourly intervals, the standard deviation is likely to undergo circadian changes related to the wave form of the circadian rhythm in heart rate itself: a larger variability is anticipated and found around awakening, when heart rate changes rather abruptly from low nightly to much higher daily values (the actual transition usually starts earlier, but any anticipatory rise preceding awakening and the transition in the

evening are usually smoother and slower). These considerations further credit the results of Huikuri et al¹: By computing the standard deviation of RR intervals over 5-minute spans and averaging hourly, the interference by the circadian wave form of heart rate with the variability of RR intervals as such is reduced. The antiphase between the rhythms in heart rate and its variability is thus unlikely to be a consequence of the wave form of the circadian heart rate rhythm.

To check on the properties of the standard deviation as a function of the interval over which it is calculated and to rule out any artifact in the rhythmicity of heart rate variability reported by Huikuri et al,¹ computer simulations were performed. Beat-to-beat heart rates over 24 hours were simulated using the 3-component model of Table I, contaminated with a normally distributed error term of zero mean and constant variance. As expected, the standard deviation calculated over the whole 24-hour span approximates the circadian amplitude: that which is calculated over consecutive hourly spans undergoes a circadian rhythm with an acrophase around awakening, whereas that calculated over consecutive 5-minute spans and averaged hourly does not exhibit similar changes. The fact that the 2 rhythms have an almost opposite timing, as reported for heart rate¹ and earlier for blood pressure,⁴ is also in keeping with the negative correlation between heart rate variability and heart rate itself, re-

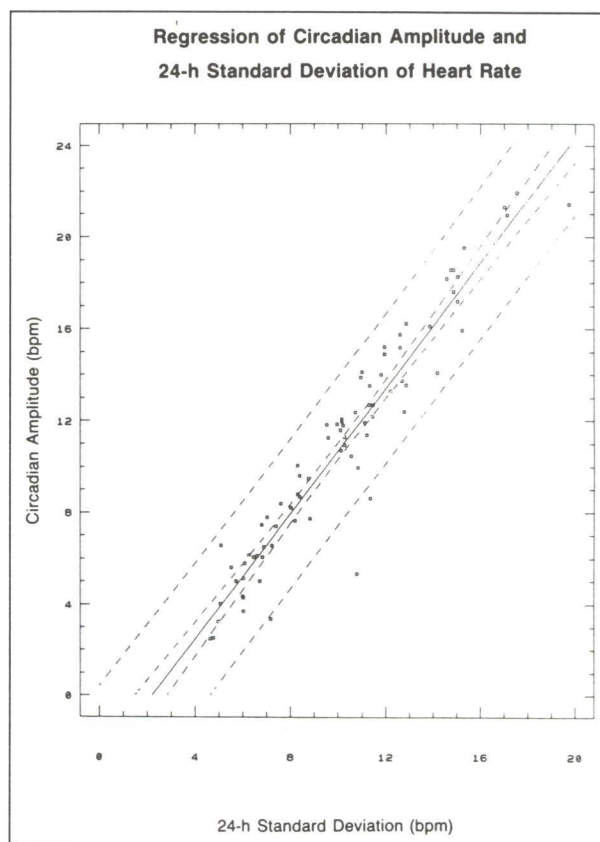


FIGURE 2. Circadian amplitude correlates positively ($r = 0.946$; $p < 0.001$) with the overall standard deviation. Computations from hourly averages of heart rates measured every 7.5 minutes over 24 hours on 40 men, 20 to 60 years of age, monitored on 2 occasions.^{7,8}

ported by both Kleiger et al⁵ and Rich et al,⁶ who, without reference to timing, derive benefit from using data covering an entire circadian cycle.

Aberrant heart rate variability may reflect alterations in cardiac autonomic tone, which could predispose to the development of lethal arrhythmias.⁶ In this context, the quantification of a time structure in heart rate variability serves for facilitating the recognition of any early deviation that may point to an increased cardiovascular disease risk. Beyond the context of a mechanism for the inverse relation between heart rate and its variability and its bearing on sudden cardiac death, an earlier finding made with chronobiologic methods gains in interest: An increased incidence combined with an amplified, phase-shifted circadian rhythm of premature ventricular beats in a 24-hour electrocardiogram performed after a myocardial infarction characterizes patients who die suddenly within 5 years compared with those who survive (Figure 3). The groups were separated by considering the features of the circadian rhythm, but not when only the average 24-hour incidence of ventricular premature beats was used. Variability without or preferably with chronobiom-

etry² may add another dimension, unavailable for the retrospective Figure 3 analyses. The time structure of variability within the physiologic range remains the challenge of an already rewarding chronocardiology (Figure 3). The incidence of infant as well as adult sudden death reveals a spectrum of population rhythms that should prompt research into the factors underlying the difference in pattern illustrated in Figure 3.

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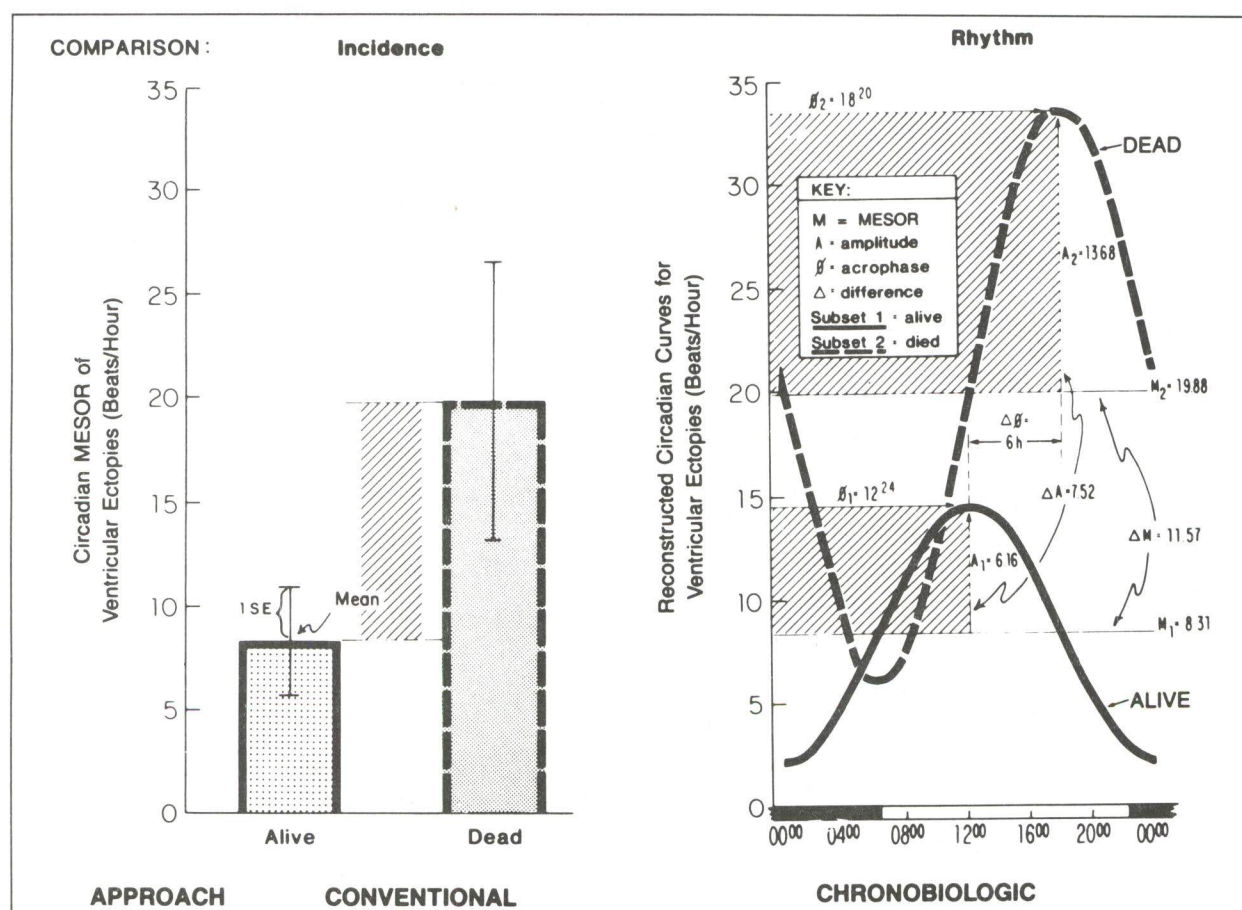


FIGURE 3. Chronobiologic analyses based on the circadian amplitude and acrophase in addition to the 24-hour mean value of hourly incidence of ventricular ectopies in 24-hour ECG succeed ($p = 0.002$) in separating groups of patients who are dead or alive 5 years after a myocardial infarction when the conventional approach (left) based only on the 24-hour mean does not ($p = 0.084$). Adapted with permission from Orth-Gomér K, Cornélissen G, Halberg F, Sothorn R, Åkerstedt T. Relative merits of chronobiologic vs. conventional monitoring of ventricular ectopic beats. In: Halberg F, Reale L, Tarquini B, eds. Second International Conference, Medico-Social Aspects of Chronobiology, Florence, Oct. 2, 1984. Rome: Istituto Italiano di Medicina Sociale, 1986;767-770.

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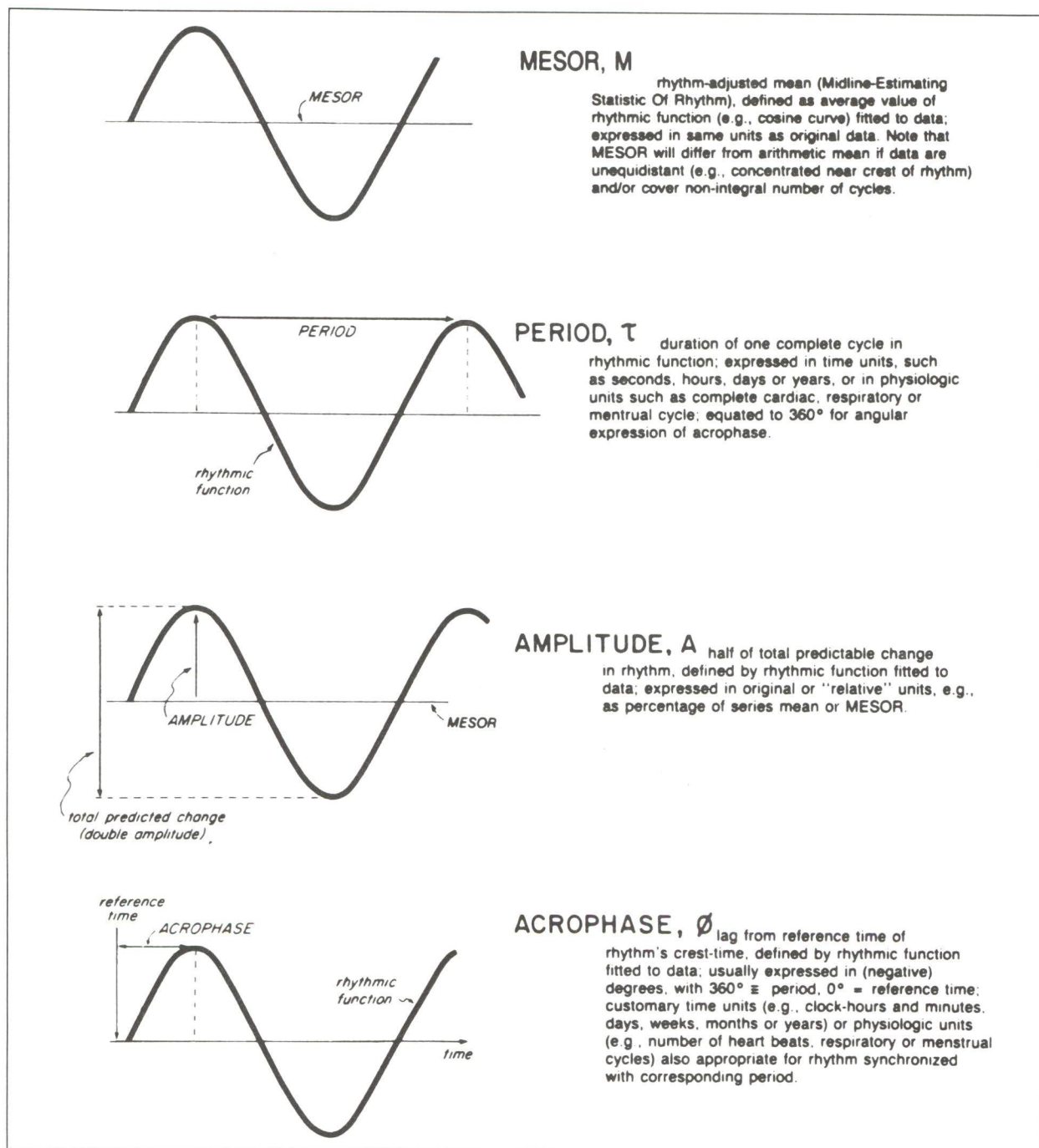
APPENDIX

Definition of Terms (Figure 4)

Cosinor: statistical summary with display on polar coordinates of rhythm characteristics. The single cosinor adjusts, by

least squares, a rhythmic function with a presumed period (anticipated on the basis of prior experience) to a data series, thus providing point-and-interval estimates of MESOR, amplitude and acrophase; statistical significance of the fitted function is checked by means of a zero-amplitude test. The population mean cosinor derives inferences for the population from parameter estimates obtained from 3 or more individuals or from 3 or more time series obtained from the same individual.

MESOR: an acronym for the midline-estimating statistic of rhythm; rhythm-adjusted mean, defined as the average value of a rhythmic function fitted to the data. The MESOR differs from the arithmetic mean whenever the data are nonequidistant and/or cover a non-integral number of cycles, in which case the



MESOR is usually more accurate (i.e., associated with less bias from sampling). When data are equidistant, the MESOR is also usually more precise (i.e., associated with a smaller standard error) if the time series undergoes a rhythmic change.

Period: duration of 1 complete cycle of the rhythmic function.

Amplitude: half the total predictable change defined by the rhythmic function fitted to the data.

Acrophase: lag from a given reference time (such as midnight) of the rhythm's crest time, defined by the rhythmic function fitted to the data. The acrophase is expressed in (negative) degrees, with 360° equated to the period length and 0° taken as the reference time. In the case of circadian (24-hour)

rhythms, when 0° is chosen at midnight, the acrophase can also be expressed in hours and minutes.

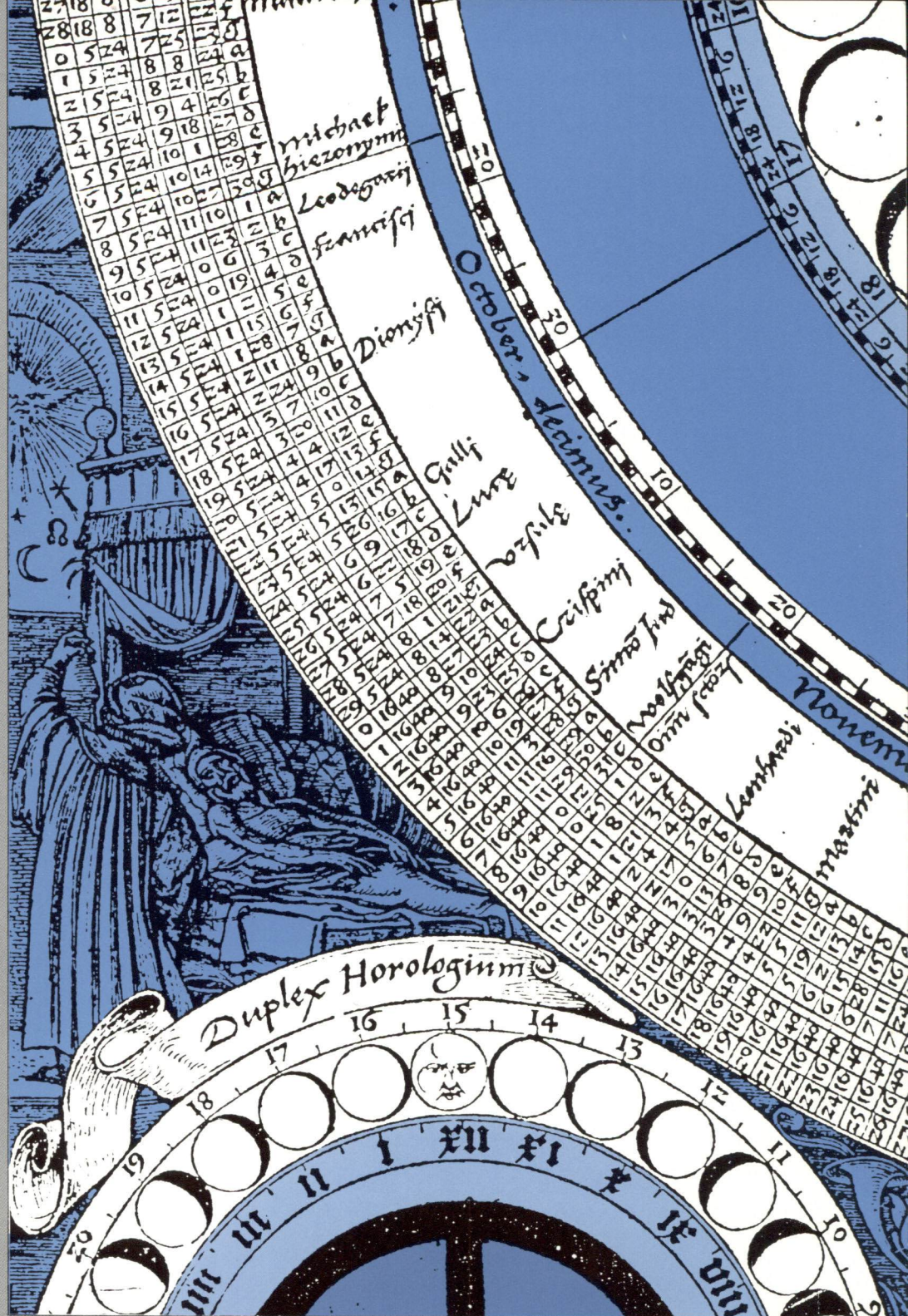
Circadian: relating to biologic variations or rhythms with a frequency of 1 cycle in 24 ± 4 hours.

Ultradian: relating to biologic variations or rhythms with a frequency higher than circadian (i.e., with a period shorter than 20 hours).

Harmonic: any periodic function with a given period, τ , can be considered as the sum of a constant term (MESOR) and sinusoidal functions with periods $\tau, \tau/2, \tau/3, \dots$, with given amplitudes and acrophases. The component with a period τ is the fundamental or first-order harmonic. The component with a period τ/n is the n th harmonic, where $n = 2, 3, \dots$

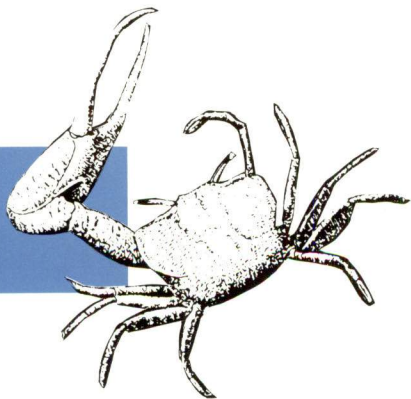
For everything
there is a season
and a time for
every matter under
heaven: a time to be
born and a time to
die; a time to plant
and a time to pluck
up what is planted.
God has made
everything beautiful
in its time.

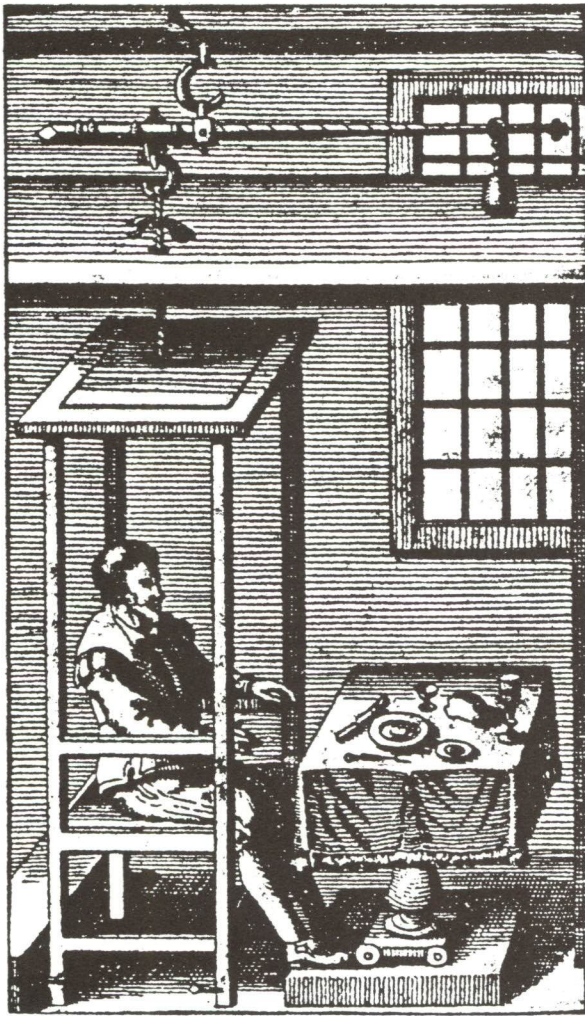
— Ecclesiastes



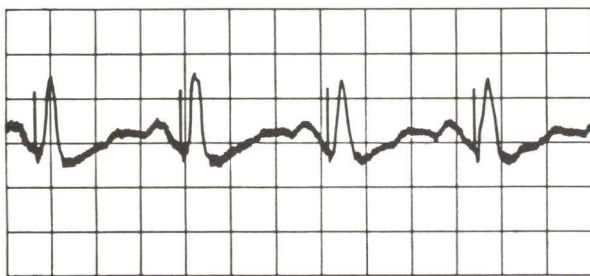
CHRONOBIOLOGY

A SCIENCE IN TUNE WITH
THE RHYTHMS OF LIFE





Sanctorius on his balance



Rhythmic characteristics of the heartbeat can reveal a patient's state of health.

In 1647, the Italian scientist Santorio constructed a huge balance, where he could sit each day as he took his meals. For roughly 30 years, he weighed and measured himself, noting changes in his physical condition. He found that his weight fluctuated with a monthly rhythm that paralleled a 30-day cycle in the turbidity of his urine.

What Santorio did was to document that even physiological changes echo the message of Ecclesiastes: "For everything there is a season. . . ."

More recently, researchers have recognized that through evolutionary time, environmental cycles have left their stamp on the basic biology of organisms. Living creatures not only follow the rhythms of seasonal change, but also possess their own intrinsic rhythms. The daily alternations of light and dark, the yearly changes in day length, the rhythms of the tides synchronize, but do not drive these intrinsic rhythms.

Rhythms we can see in nature range from the night-hunting habits of owls to the day-hunting efforts of hawks. Bees use the sun's position to find their way between food and hive. In doing so, they use a built-in sense of time to compare the sun's changing place in the sky with their own whereabouts. And so precisely do some flowers time their opening and closing that the 18th-century botanist Carl Linnaeus was convinced that a knowledgeable botanist without a watch could tell time by noting which flowers were open or closed.

Inside the body are other rhythms. Brain waves oscillate with periods of milliseconds; the heart pulses rhythmically some 70 times each minute. Body temperature and blood pressure both rise and fall with a 24-hour rhythm. Hormone levels fluctuate monthly and seasonally. In the skin, cell division peaks by night and drops markedly by day.

Studying biological time structures like these, learning what determines them, and how they change under different conditions is the domain of a new science: chronobiology. Named by University of Minnesota Medical School professor Franz Halberg, the term refers to the cyclical view of time held by the ancient Greeks. Chronobiologists look for patterns or rhythms that repeat themselves cyclically.

Such rhythms may have profound implications for the practice of medicine. Chronobiologists have found that timing may be of immense importance in the detection, treatment, and prevention of disease.

As Halberg has observed, trying to accurately assess something like high blood pressure using a single measurement or even a series taken at arbitrary times in the physician's office is like taking "snapshots of a roller coaster."

"Blood pressure fluctuates rhythmically," he points out, "not only during a given 24 hours, but also from day to day."

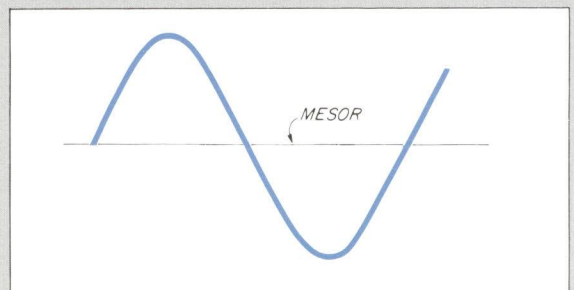
"Unless we monitor for a 48-hour period and then interpret the data properly, we may treat people who simply have 'white coat' or office hypertension. We may unnecessarily give a patient drugs that render him impotent or give him gout. We may give him a stigma

SOME TIMELY WORDS

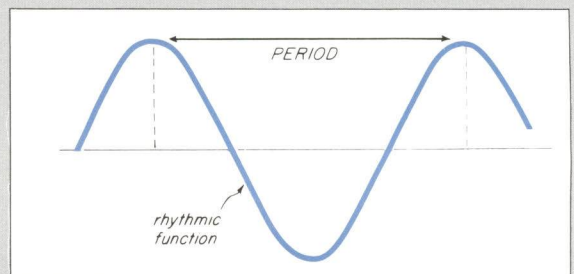
Chronobiology has a language of its own, designed to describe the characteristics of rhythms. Here are a few examples.

MESOR: (Midline Estimating Statistic of Rhythm)

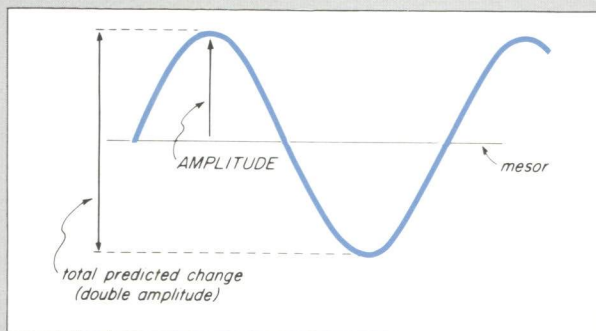
The average value of a cosine curve fitted to the data a chronobiologist has taken, usually the half-way point between the peaks and troughs of the cosine curve. The MESOR can be, but isn't always, the same as the arithmetic mean. If, for example, most of the data are clustered around the peak of the curve, because the researcher gathered more data at this time, the arithmetic mean will be much higher than the MESOR.



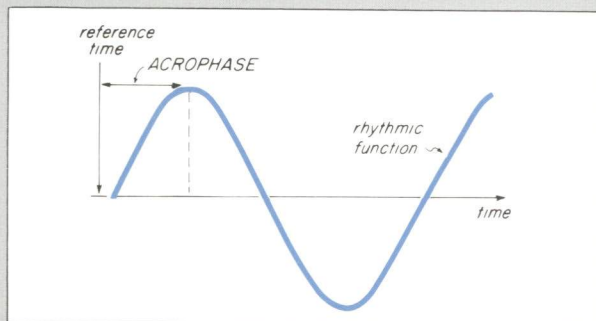
PERIOD: The duration of one complete rhythmic cycle, measured from peak to peak, or from one reference time to the next, as from midnight to midnight in a 24-hour period.



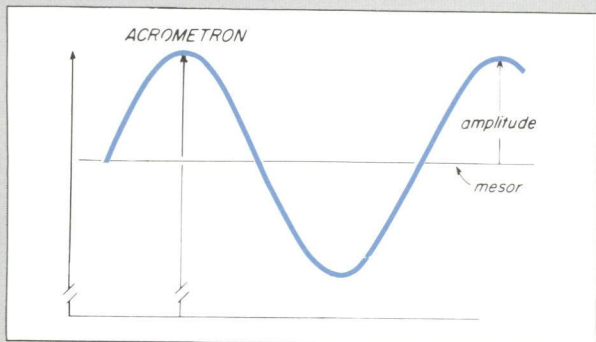
AMPLITUDE: Half of the total predictable change in a rhythm.



ACROPHASE: The lag between the reference time (midnight, or 0000 hours in a 24-hour day) and the time of the rhythm's crest.



ACROMETRON: The measure of the highest predicted value of a rhythm (BATHYMETRON refers to the lowest measure).



CIRCADIAN RHYTHM: A rhythm approximately 24 hours in length.

INFRADIAN RHYTHM: A rhythm of more than 28 hours. Examples include the half-weekly (circasemiseptan) cycle of sudden human death. Most sudden cardiac deaths occur on Monday, with a second peak on Thursday.

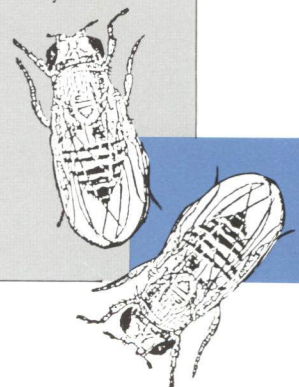
ULTRADIAN RHYTHM: A rhythm with a period of less than 20 hours. Examples include the sleep/wake cycles of patients with narcolepsy, a sleep disorder in which patients fall asleep several times daily.

CIRCASEPTAN RHYTHM: A rhythm with a period of about a week. Some hormonal rhythms follow a roughly weekly cycle, as do patterns of kidney transplant rejections. According to Halberg, kidney transplant rejection episodes are more likely to occur on the 7th, 14th, 21st, or other 7-day intervals after operation.

CIRCATRIGINTAN RHYTHMS: Rhythms, such as the human menstrual cycle, that approximate a month in duration.

CIRCANNUAL RHYTHMS: Rhythms with a period of about a year. Seasonal rhythms and reproductive rhythms in some animals follow a circannual cycle.

MACROPHASE: The highest value among the individual data points or averages of data points. This high value may be fortuitous or may be important.



of bad health for life or place his job in danger.

"The reverse is also true. We may miss abnormal readings in patients who have high blood pressure only at night."

Similar arguments hold for timing cancer chemotherapy to periods when tumor cells are most vulnerable or normal tissues most resistant. Proper timing can significantly reduce the toxicity of the drugs for healthy tissues and maximize their attack on tumor cells.

Environmental Cycles Coordinate Biological Cycles

Cyclical behavior in cells and organisms may be as old as life itself. Chronobiologists speculate that evolutionary forces shaped biological rhythms, selecting for organisms that had the ability to synchronize their activities to environmental rhythms.

"Any study of the importance of time in biology focuses quickly on cyclic behavior, the tendency of organisms to repeat their activities in time," explains Franklin Barnwell, professor of ecology and behavioral biology at the University of Minnesota. "Some of the most striking of these repetitions reflect environmental cycles."

Until recently, researchers assumed that environmental cycles were the driving force behind cycles in organisms. Today it seems clear that biological rhythms are built into organisms, programmed into their genetic material as surely as the ability to spin webs,

SETTING CYCLES DOWN ON PAPER

To describe and analyze rhythmic patterns, chronobiologists turn to statistics. With the help of computers, they look for the rhythmic mathematical function that best describes or approximates the data. Usually they choose the cosine because the cosine of zero, being one, acts as a handy phase reference. Even better, it allows scientists to present their data in a chronological way.

Here's an example. The curves on page five show measurements of systolic blood pressure in a healthy woman. Each graph represents all the data taken over six days compiled to form one idealized 24-hour period. The dots in the upper left-hand curve represent individual measurements. The bar graphs represent the hourly means for all measurements. Each of the succeeding graphs demonstrates one of the circadian characteristics defined above. The heavy black line in each graph is the best-fitting cosine function approximating all the data.

The circular figure shows similar data, measurements of blood pressure in a healthy woman taken approximately every 10 minutes over many days. This time, the data are presented in a *paradesm* — a clocklike presentation several steps removed from the original data.

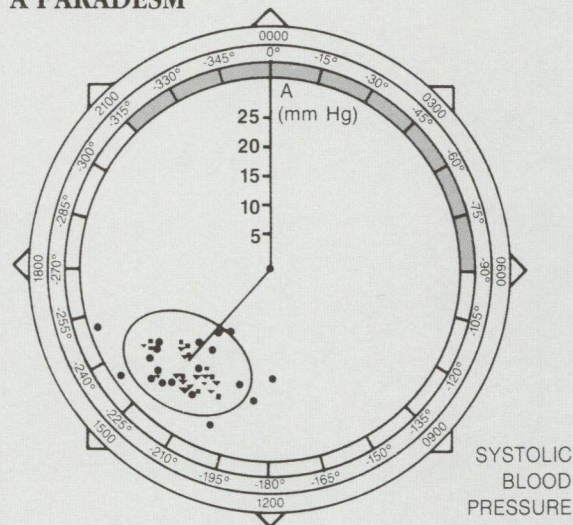
The 24-hour period is represented as a circle, with hours and degrees beginning at 0000. The acrophase, or peak of the rhythm, falls at about 1500 hours (3 pm), or -220° on the circle. The average amplitude of the rhythm at its peak is shown by the length of the clock hand. The symbols (●, ■, ▼) show the blood pressure amplitudes and acrophases taken during 24-hour measurements (●), 48-hour measurements (■), and more than 48-hour measurements (▼).

The ellipse shows a region in which the acro-

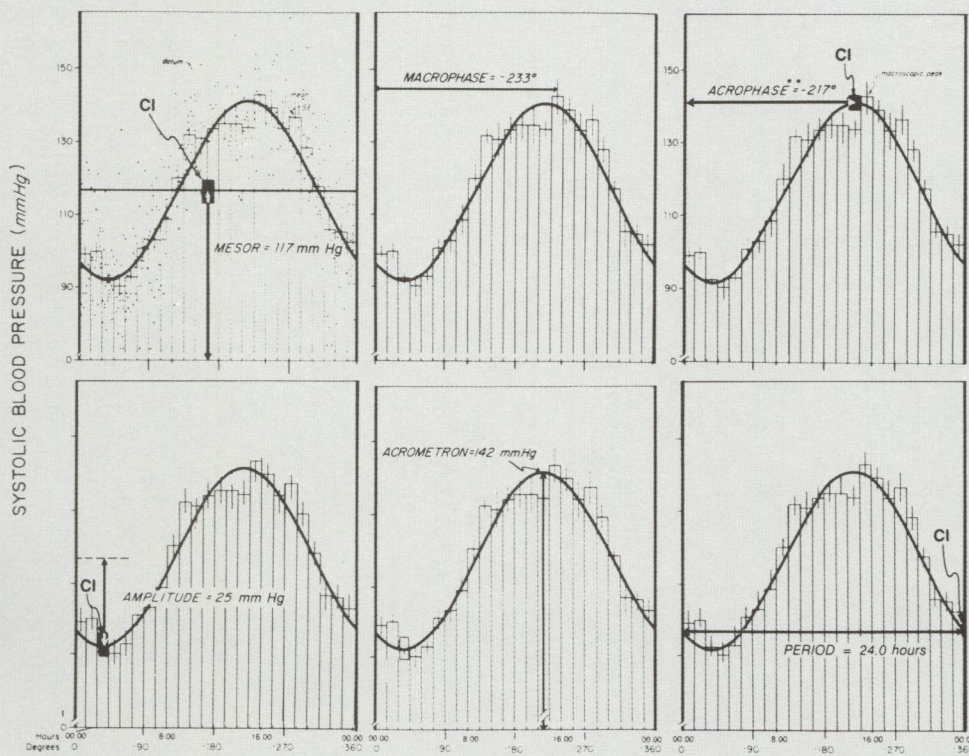
phase and amplitude of this woman's blood pressure will fall 90 percent of the time. As you can see, one-day measurements often fall outside this region, suggesting that a 24-hour period is too short to give an accurate picture of a patient's blood pressure pattern. Measuring for 48-hour spans and analyzing them by this method allows a physician to discount short-term high blood pressure measurements resulting from a fast tennis match or an altercation with a surly cab driver. Dark and light areas on the circle show sleep and wake periods.

One advantage of this kind of presentation is that the circle can represent an hour, a day, a year, or an eon.

A PARADESM



DAILY BLOOD PRESSURE CHANGES IN A HEALTHY WOMAN



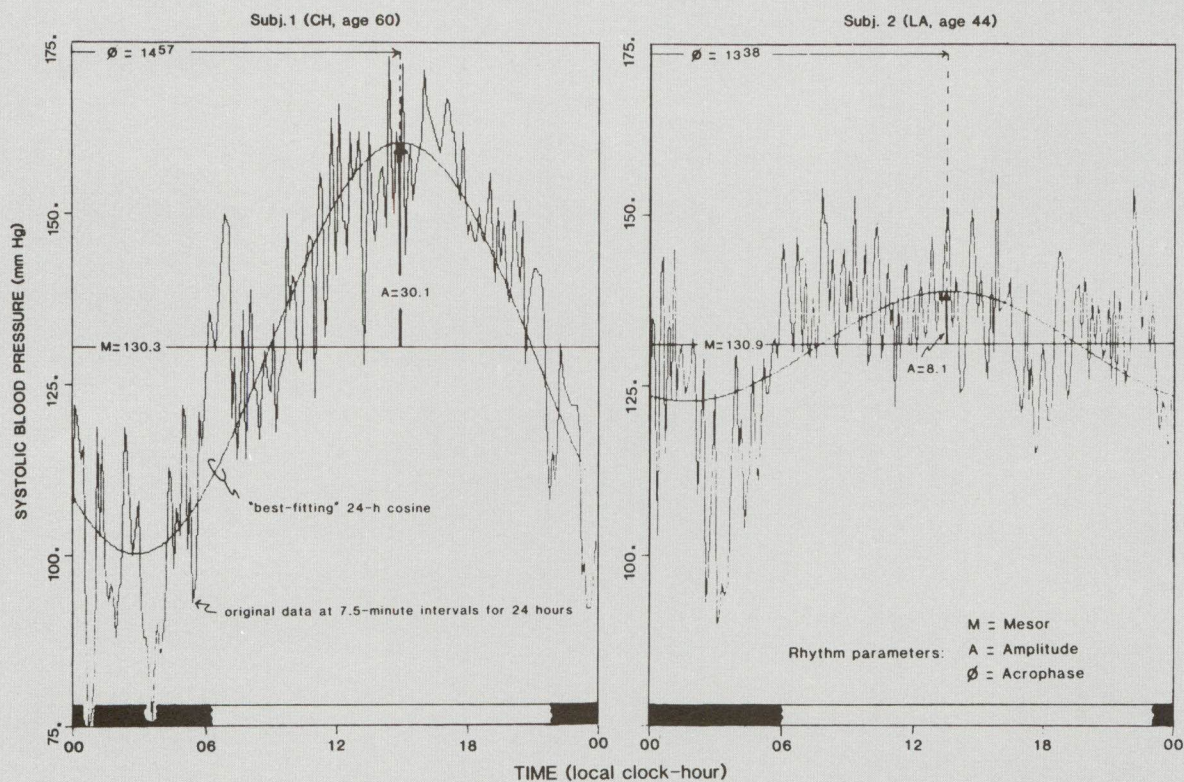
* From healthy women 60 yrs of age

** Zero-time = 00°° clock hours

TIME ON CYCLE**



DAILY CHANGES IN SYSTOLIC BLOOD PRESSURE IN TWO HEALTHY MEN



*Each wearing Pressurometer III from Delmar Avionics (Irvine, CA) for 24 hrs

As these graphs of systolic blood pressure show, different people have distinct rhythmic profiles. Here, the amplitudes of the two rhythms are markedly different, yet the MESOR (M in the figure) is the same. Understanding normal rhythms in such functions as blood pressure may help identify people at risk for certain diseases. As chronobiologist Franz Halberg points out, "The period, amplitude, and/or acrophase of a

rhythm may change with the risk of developing a disease—in the absence of any increase in the mean."

Furthermore, as these graphs illustrate, a single blood pressure reading taken in the morning gives little indication of what a patient's blood pressure is like during its daily peak. Some patients have abnormally high blood pressures only at night.

make nests, or defend their young.

The first suggestion that chronobiologic rhythms are built into living creatures came from French scientist J.J. de Mairan in 1729. De Mairan wondered whether the heliotrope plant, which turns on its stem to face toward the sun, would stop its movements in constant darkness. To his surprise, the plant continued its daily motions, just as though it were following the sun's movement across the sky.

One hundred fifty years later, a German investigator, Wilhelm Pfeffer, repeated the experiment with *Mimosa* plants, which droop during the night. He too found that the daily cycle of leaf movement continued even in constant dark or constant light. Finally, in the 1950s, Halberg found that the number of white blood cells in mice rises and falls with a daily rhythm. Further, removing the adrenal glands obliterated this rhythm as well as others. Since then, researchers have found that living creatures pulse with physiological rhythms.

Investigators now define a number of chronobiological rhythms. Ultradian rhythms, such as heartbeat, are cycles of less than a day. Circadian rhythms, such as the sleep/wake cycle of 8/16 hours and the daily temperature cycle, are roughly 24 hours in length. Cycles of about 7 days are called circaseptan, those of about 29 to 30 days are called circatrigintan, circamensan, or circalunar; yearly or seasonal rhythms are termed circannual rhythms.

Characteristic of all these rhythms — and definitive — is the fact that they continue even when the organism is isolated from normal cyclical environmental cues. If a researcher changes the dark/light schedule for an animal or plant, he or she can shift the

rhythms of sleep, activity, body temperature, even reproduction.

In constant (noncyclical) conditions in the laboratory, however, an organism's rhythmic behavior gradually drifts out of synchrony with the environment. Biologists call this *free running*. The term, suggested by engineer and Medtronic founder Earl Bakken, comes from physics where it's used to describe an oscillator, such as a clock pendulum, that assumes its own rhythm once the clock weights are raised and the pendulum begins to swing.

Nineteenth-century Europeans settling in tropical South America inadvertently created an experiment that demonstrated free-running rhythms. Many of these colonists planted European trees to remind themselves of home. But in the tropics, there is little seasonal change; day length is the same year round. At first, the trees dropped their leaves, went dormant, budded out, and bloomed as if they were still in Europe. Eventually, however, they lost their synchrony with European seasons and drifted into a free-running rhythm.

In 1962, a Frenchman, Michel Siffre, entered a cave to live for two months isolated from daily cycles of night and day. In that time, he discovered that he adopted a daily routine of activity and rest that ran approximately 25 hours, rather than the 24-hour period to which he had been accustomed all his life. Similar experiments run by Dr. Jurgen Aschoff, director of the Max Planck Institute for Physiology, show that people living under constant conditions in specially constructed bunkers often free run on a roughly 25-hour day, although some settle on cycles that range anywhere from 16-hour days to 30-hour days.

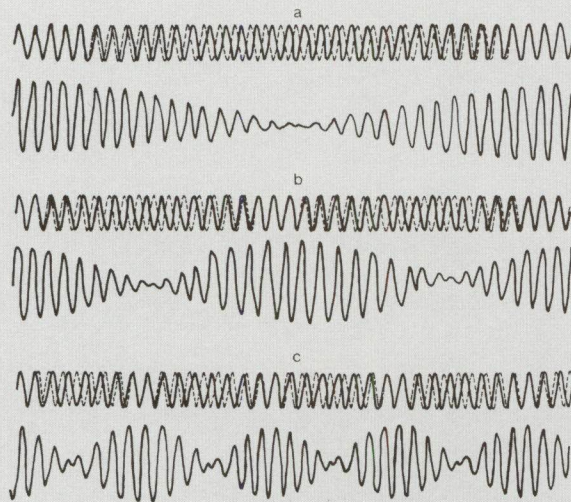
These experiments in humans echoed an earlier study in mice, run by Halberg in the early 1950s. He looked at rhythms in body temperature and in white blood cell count in two groups of mice, blind and sighted. In sighted mice, these rhythms rose and fell at the same times every day. In blind mice, on the other hand, the rhythms shifted, peaking earlier each day. "The only explanation," Halberg says, "was that the cycling regimen of light and dark could not synchronize these rhythms in blind animals."

Are biological rhythms learned? Researchers don't think so. Learned rhythms would persist for a time, shift, and then die out. In

contrast, when biological rhythms are uncoupled from environmental control, they continue to oscillate, but at their own rates. Halberg's blind mice, for instance, developed temperature cycles that were distinct for each mouse, suggesting the animals had their own genetic patterns for rhythm.

Fruit flies, as another example, have a developmental life cycle of about two weeks. An egg hatches into a larva within a few hours of laying. The larva grows for about seven days and then enters a deceptively dormant-looking state, the pupa. During the three days it is pupating, the larva's structures are essentially torn down and rebuilt into adult form.

HOW TWO RHYTHMS FORM A THIRD



These models show how two rhythms can interact to form a third. In a, b, and c, you can see that two rhythms add together when their peaks coincide. When their peaks are out of phase, the two influences cancel each other out. Together, the interactions of the first two rhythms form a

third, whose characteristics are determined by how much the first two differ.

Halberg has suggested that manic-depressive patients, who experience mood swings every few weeks, could be victims of a similar interaction of two groups of as-yet-unidentified circadian rhythms. One of these may be synchronized to the 24-hour day/night cycle while the other "free runs." Together they could create a third pattern in the patient's biochemistry that could produce periodic swings in mood.

Models like this owe a debt to studies of marine animals. For example, fiddler crabs darken during the day and turn lighter at night, a color change that may protect them from sunlight and predators. Crabs are darkest during the daytime low tide, which shifts by 50 minutes each day.

Researchers have found that fiddler crabs have both a 12.4-hour metabolic rhythm that corresponds to tidal intervals and a 24-hour rhythm. Together, the two rhythms interact to form a third, 15-day cycle in which the crabs assume their darkest hue at the same hour as they did 15 days earlier.

Adult flies emerge from the pupa in synchrony at dawn.

“But if flies are reared in complete darkness, generation after generation, you get flies emerging at all times of the day,” Barnwell explains. The flies’ intrinsic rhythms are no longer synchronized to environmental rhythms. The right environmental cue, however, will bring their developmental cycles back in synchrony.

“If you expose the flies to a brief flash of light, 24 hours later you see a synchronized emergence of flies from the pupal cases,” Barnwell adds. “Since the flies cannot learn the length of day from the brief flash, this piece of evidence suggests that some kind of clock, not learning, guides these organisms. Then, if you return the flies to complete darkness, you find that the rhythms of emergence gradually drift over several generations.”

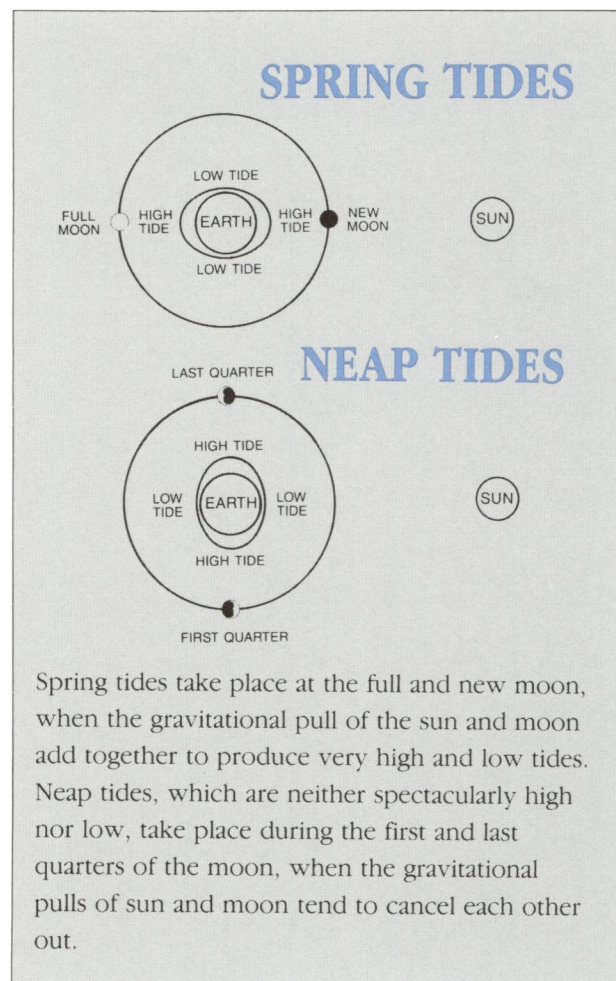
While these intrinsic rhythms are synchronized by environmental rhythms, they also interact with each other to produce variations on rhythms.

For example, plants and animals that live at the edge of the sea need to gear their activity, feeding, and reproduction to two different environmental rhythms: the rise and fall of the tides and the rising and setting of the sun. Both cycles are caused by the earth’s turning on its axis, exposing its face to the sun and moon once during each daily rotation.

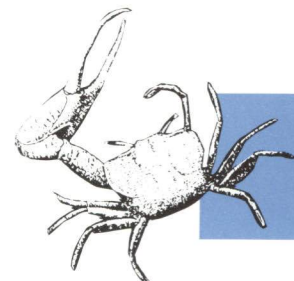
Twice each lunar month, the sun and moon are in line — at the full and the new moon — and the sun’s gravitational pull added to the moon’s causes tides that are considerably bigger than average. Called spring tides, these tides take place every 15 days — year round. They result from the interaction of two

environmental rhythms, the daily rotation of the earth on its axis and the 29.5-day rotation of the moon around the earth.

Plants and animals that contend with these changes must have both a daily time sense and a tidal time sense. “Intertidal animals react to the tidal peaks every 12 hours and 25 minutes,” Barnwell explains. “But they



Spring tides take place at the full and new moon, when the gravitational pull of the sun and moon add together to produce very high and low tides. Neap tides, which are neither spectacularly high nor low, take place during the first and last quarters of the moon, when the gravitational pulls of sun and moon tend to cancel each other out.



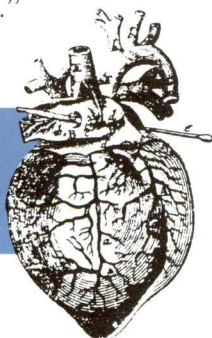
also have a 24-hour rhythm because they respond to the light/dark cycle. Together these two rhythms interact to cause a third, 15-day cycle, which correlates with the spring tide cycle. This 15-day cycle may be important in reproduction, when fiddler crabs, for example, release their eggs at the high spring tides.”

Many organisms that live between the tides have intrinsic rhythms that correspond to the 15-day spring tide cycle. The brown alga, *Dictyota dichotoma*, sheds its reproductive cells into the waters of a high tide on a roughly 15-day cycle. A marine midge, *Clunio marinus*, emerges, mates, and lays its eggs on the red algae growing at the lowest limit of the lowest tides. Since the algae are exposed only once each 15 days, the midge has but two hours or so to complete its entire adult life — a life cycle with a roughly 15-day rhythm that persists even under constant conditions in the laboratory.

Rhythms Are Inherited

How rhythms are built into organisms, no one really knows. What is clear is that they are inherited, programmed into the genetic blueprint of the organism.

“Rhythms,” according to Halberg, “are the products of genes not just in space but in time.”



The circadian rhythms of stem and leaf movements in two stocks of bean plants differ; if the two strains interbreed, their offspring show a circadian rhythm in between those of the parents. “And if you monitor such rhythms as heart rate in identical human twins who have been reared apart,” Halberg observes, “you can document that the characteristics of the rhythms are inherited.”

Researchers have also learned about how rhythmic behavior is inherited by studying that standard laboratory organism, the fruit fly. Not only is fruit fly biology well known, but investigators can study many generations in a short time. What’s even more intriguing, analysis of the genes thought to govern chronological rhythms in fruit flies shows that they are very similar to certain human genes.

One genetic researcher, Clarkson University professor Ronald Konopka, has looked for variations in the gene that governs biological rhythms in fruit flies. According to a review in *Science* magazine (December 1985), he has found three genes that affect two prominent rhythms in the flies. One rhythm governs the time that new flies emerge from the pupa. The other controls the pattern of the mating song, which in normal flies repeats every 60 seconds.

One gene mutation seems to produce a race of insomniacs — flies that emerge from the pupa at any time of day or night. Their mating songs have no discernible rhythm. Another variation produces flies that seem to run on a short day, 18 to 20 hours. Their mating songs repeat every 40 seconds. The third variant has 28- to 30-hour days and mating songs with 80-second intervals.

Another investigator, Michael Young of

RHYTHMS TAKE PLACE AT MANY LEVELS



Chronobiologists are finding rhythms at many levels in biology. Chemical reactions, the physiology and behavior of single-celled organisms, cell cultures, organs, multicellular organisms, families, and societies all display cyclical behaviors. These can range from enzyme interactions in cells and test tubes to such social influences on sleep patterns as siestas in Spain and Italy or breakfast meetings in corporate America.

What's more, within a complex multicellular organism such as a human being, rhythms interact to create new rhythms. Influences from an individual's hormone systems, cycles of cell growth and repair, and nervous system interact with family routines, seasons, and such societal oddities as shift work or jet travel.

Rockefeller University, together with Konopka, found that snipping out the strand of DNA that holds the rhythm gene produces flies that have no apparent rhythms. Most recently, Young has found that the gene, called the *per* gene for *period*, codes for proteins in the cell that regulate rhythms. The more of these proteins a fly makes, the faster its cycles run — the shorter its day, the faster the beat of its mating song. What's more, Young and his colleagues have discovered similar DNA coding in humans, mice, and chickens.

Knowing about the *per* gene gives us some clues about how rhythms originate in cells and tissues. Some researchers suggest that the membranes around living cells, which allow some ions (electrically charged atoms and molecules) to enter and leave, and bar entry to others, may be the time counter. As ions move across cell membranes, the electrical potential across the membrane changes, perhaps triggering a rhythmic oscillation.

Support for this idea comes from the fact that chemicals, such as ethanol, alter the permeability of membranes and also slow or even shift circadian rhythms in plants and animals. According to this hypothesis, the *per* gene may regulate the opening and closing of ion channels in the membranes, thus regulating rhythms.

Young's evidence, however, shows that proteins coded by the *per* gene are of a rare type, one not associated with ion channels. "Perhaps we're dealing with a molecule that governs interactions of groups of cells that in turn form a clock," Young suggested in *Science* magazine (December 1985).

Other researchers hypothesize that oscil-

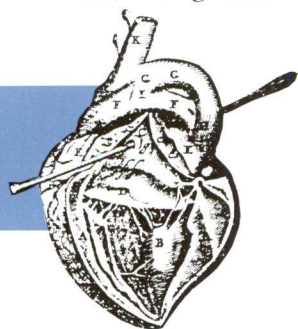
lations in biochemicals in the cell lead to rhythmic interactions that in turn drive the larger rhythms we see. While this idea is intriguing, so far there's little evidence to support it.

Finally, the Chronon hypothesis places the driving force for biological rhythms in the genetic material in the cell's nucleus. Researchers who favor this idea propose that circadian periods are measured out by a continuous reading of the genetic code held in a long loop of chromosomal DNA. According to Barnwell, "Proponents of this view believe the clock is the sequential reading of a DNA strand."

Whatever the timing mechanism, it's increasingly clear that biological timekeepers exist, are genetically controlled, and are important factors in the biology of organisms. Where they may be most important is in dealing with people who are ill.

CHRONOBIOLOGY IN MEDICINE

Hearth attacks strike three times more often at 9:00 in the morning than at 11:00 at night, according to findings reported in *The New England Journal of Medicine* (November 1985). Testicular seminoma, the most common cancer in men under 35, is diagnosed far more often in



winter than in summer. The body temperature cycle of a depressed patient may run on an earlier schedule than the same cycle does in a healthy person, according to a review in the *American Scientist* (January 1986).

These findings underscore the message chronobiologists are teaching to medicine: *when* you treat a patient may be as important as *how* you treat a patient. Chronobiological cycles may be immensely important in diagnosing, treating, and even preventing disease.

Using Chronobiology to Diagnose Disease

In diagnosing cardiac problems, physicians of the future will monitor patients with arrhythmias for extended periods to ascertain daily or even weekly electrocardiograph (ECG) patterns.

"The electrocardiographic assessment of the risk of sudden death is a prime concern of modern medicine," Halberg points out. Modern technology now allows a patient to wear an ECG monitor 24 hours a day. The monitor picks up patterns of arrhythmia that take place on a daily basis.

"Chronobiologic computer techniques can be applied to the 24-hour ECGs of men with coronary heart disease who die or survive within a five-year follow up," says Halberg. Patients who survive show a different pattern and timing of hourly ventricular ectopic beats from those who die from the disease during the five-year period.

Halberg believes that once physicians realize how valuable the circadian characteris-

tics of an ECG can be, they will also realize that a 24-hour reading may be too short to be satisfactory. "A patient may not show a single cardiac ischemia on the first day of monitoring, but may show a number of such abnormalities on the following 11 days," Halberg says. "For certain diseases, it may be necessary to monitor for more than 24 hours."

Using Chronobiology to Treat Disease

In treating disease, timing may be crucial. "A long list of drugs can be tolerated without obvious side effect at one time," Halberg observes, "but 12 hours earlier or later, the same dose can kill most animals exposed to it." Growth hormones stimulate cell division if they're given at one time, but have no effect at another. Because penicillin throws a monkey wrench into the machinery for building a bacterium's cell wall, the antibiotic only devastates actively growing bacterial populations.

The body's own cells go through distinct stages, taking in nutrients, making new cell materials, copying the genetic material (DNA), and then dividing. These rhythms can make or break cancer chemotherapy.

William Hrushesky, a research physician who treats cancer patients at the University of Minnesota's Masonic Memorial Hospital, observes, "A large number of drugs used in cancer therapy damage cells during different activities — DNA synthesis, cell division, or whatever. Normal tissues, like those in the gut or bone marrow, undergo DNA synthesis at one time of day, but not at another. So we try to administer a drug when it will damage

cancer cells the most and normal tissues the least.

"If you use a drug that interferes with DNA synthesis, you try to give it when the cancer cells are undergoing DNA synthesis and the normal cells are not.

"How each drug works is also important. A drug like cisplatin, for example, damages cells indiscriminantly, but the kidneys or liver handle it differently depending on the time of day. Cisplatin is much less damaging if you give it at a time when the kidneys are active and potassium excretion is high.

"Hormone rhythms — the levels of estrogen or androgen in the system — are different at different times of the day. All these rhythms affect the subcellular machinery, making a drug more effective or less effective at damaging a subcellular target."

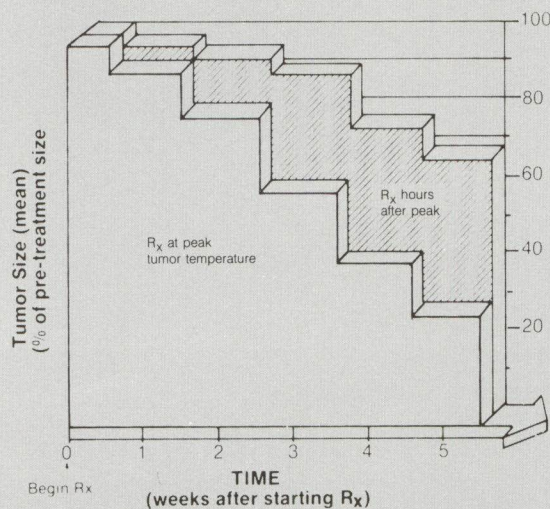
Halberg was one of the first scientists to document the importance of timing in treating cancer, whether with radiation or with drugs. He found that a dose of radiation that killed mice at one time of day was much less toxic at another time. He also found that tumor cells were more sensitive to radiation at one time of day than at another.

In the late 1960s, Halberg had a chance to put these observations into medical practice in a joint study with doctors in Chandigarh, India. "We had a group of patients who had large mouth tumors from chewing betel nut, tobacco, and lime," Halberg recalls. "These people are usually treated with radiation only."

Halberg and his colleagues looked for a marker rhythm to time their radiation treatments. The one they chose was tumor temperature, which probably reflects metabolic

CHRONORADIO THERAPY

Radiotherapy at the daily tumor temperature peak causes faster tumor regression



As this figure shows, the timing of medical therapy can make a significant difference in recovery. Radiotherapy to treat mouth tumors was given to one set of patients when their tumors were at a daily temperature peak. Within five weeks, these tumors had regressed to 30 percent of their pre-treatment size.

In patients whose tumors were treated eight hours after peak tumor temperature, however, the tumors shrank to only 70 percent of their pre-treatment size after five weeks. Furthermore, a follow-up study two years after treatment showed that over 60 percent of patients treated during peak tumor temperature were still disease free. In contrast, only about 13 percent of those treated eight hours after the peak were disease free.

activity in the tumor. The warmer the temperature, the more active the tumor cells.

"We found that treating the growths at their peak temperature led to the fastest regression of the tumor," Halberg says. "More important, a follow up two years after treatment showed that more than 60 percent of the patients treated at peak tumor temperature were still alive and disease free."

Patients treated four or eight hours before or after peak temperature did not survive as well. Only 35 percent of these patients were still alive two years later.

Using Chronobiology to Prevent Disease

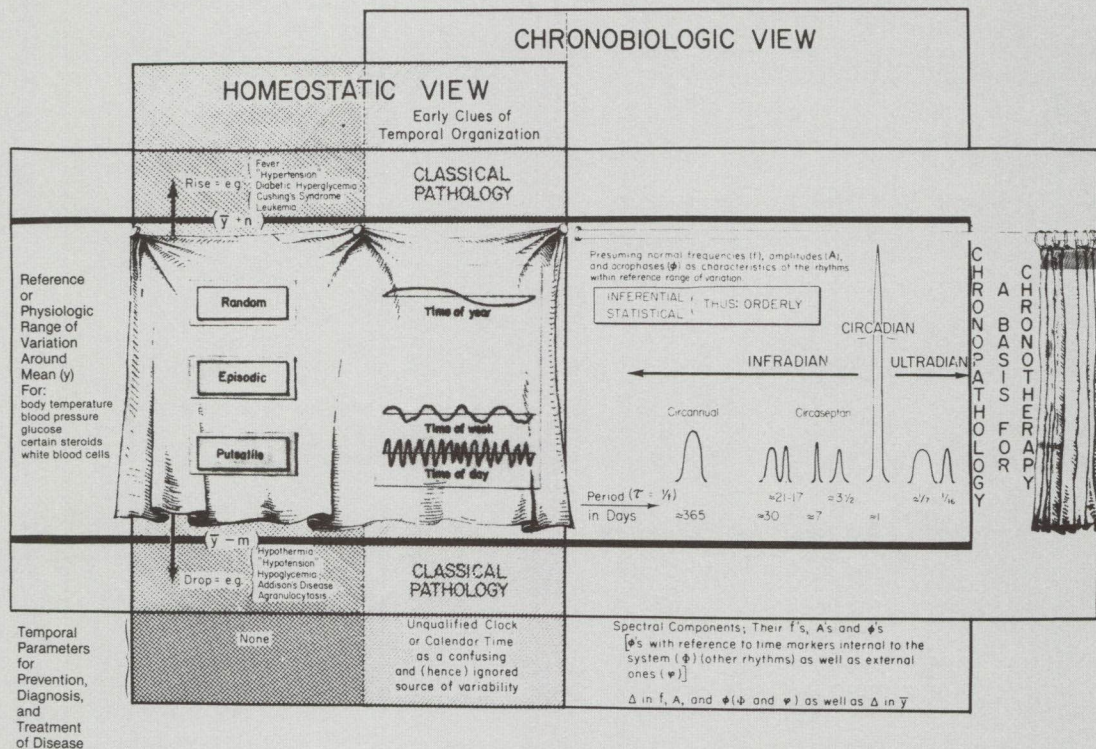


Chronobiology's greatest contribution, however, may come not from diagnosis and treatment, but from prevention of disease.

"Most important, chronobiology has taught us to use its methods to prevent major handicapping, such as high blood pressure," Halberg says. "Currently, newborn babies are given screening tests for some relatively rare diseases, such as phenylketonuria. Now the time has come to give equal emphasis to assessing the risk for major handicapping diseases, such as high blood pressure, coronary heart disease, stroke, and certain diseases of the kidney."

Working with investigators in Italy and Japan, Halberg used chronobiologic methods to study rhythmic changes in blood pressure in newborn infants. He was looking for rhythmic patterns that could predict which infants were at risk of developing high blood

TWO VIEWS OF BIOLOGY



This illustration, one of Professor Halberg's favorites, contrasts the chronobiologic view of biology with an older point of view, homeostasis. Proponents of homeostasis hold that a set of regulatory mechanisms maintains the constancy of the body's "internal milieu." Changes in biological function are counteracted or balanced to maintain an equilibrium or steady state.

Because their ability to measure physiological changes over time was limited, physiologists of the 19th and most of the 20th century could not know that the body is a sea of rhythmic changes. Although these changes take place in a predictable manner, a single measurement of, say, urinary potassium excretion or body temperature,

taken without knowing a patient's rhythm patterns, falls far short of providing an accurate picture of the patient's state of health.

In the homeostatic view, a blood pressure measurement above a certain value indicates hypertension, while a measurement below that value is a sign of hypotension. Chronobiologists, however, realize that single measurements give little information. A low or high blood pressure measurement at any one time has to be compared to known patterns of daily blood pressure cycles over time. Such cycles, harnessed to medical therapy, may open the door to new and highly effective methods for the treatment of disease.

pressure when they were older.

Halberg and his team used computers and sensors to take blood pressure and heart rate every half hour for 48 hours in a group of newborns. They then analyzed the data according to chronobiologic methods. In *Postgraduate Medicine* (January 1986), they reported that newborn infants from families with a history of high blood pressure show bigger daily swings in blood pressure than newborns from families without a history of high blood pressure. Other chronobiologic measurements also separate the two groups.

Using these methods to screen newborns, doctors can identify vulnerable infants whose families have no records of their blood pressure history. Armed with this information, physicians will be able to recommend preventive measures, such as careful diet, to prevent high blood pressure in adult life.

"What we want to do in medicine is to discover individuals or groups who have a proto- or pre-pathology," observes David Lakatua, head of endocrinology at Minnesota's St. Paul-Ramsey Medical Center. "Normally it's hard to identify people who are *destined* to develop high blood pressure, breast cancer, or other cancers. But chronobiological rhythms can help us find these people."

A look at seasonal levels of the hormone prolactin, for example, has revealed a difference between healthy women and women with fibrocystic disease, who are at risk of developing breast cancer. Normal women show a high degree of daily and seasonal change in prolactin levels. Women with fibrocystic disease show little seasonal change.

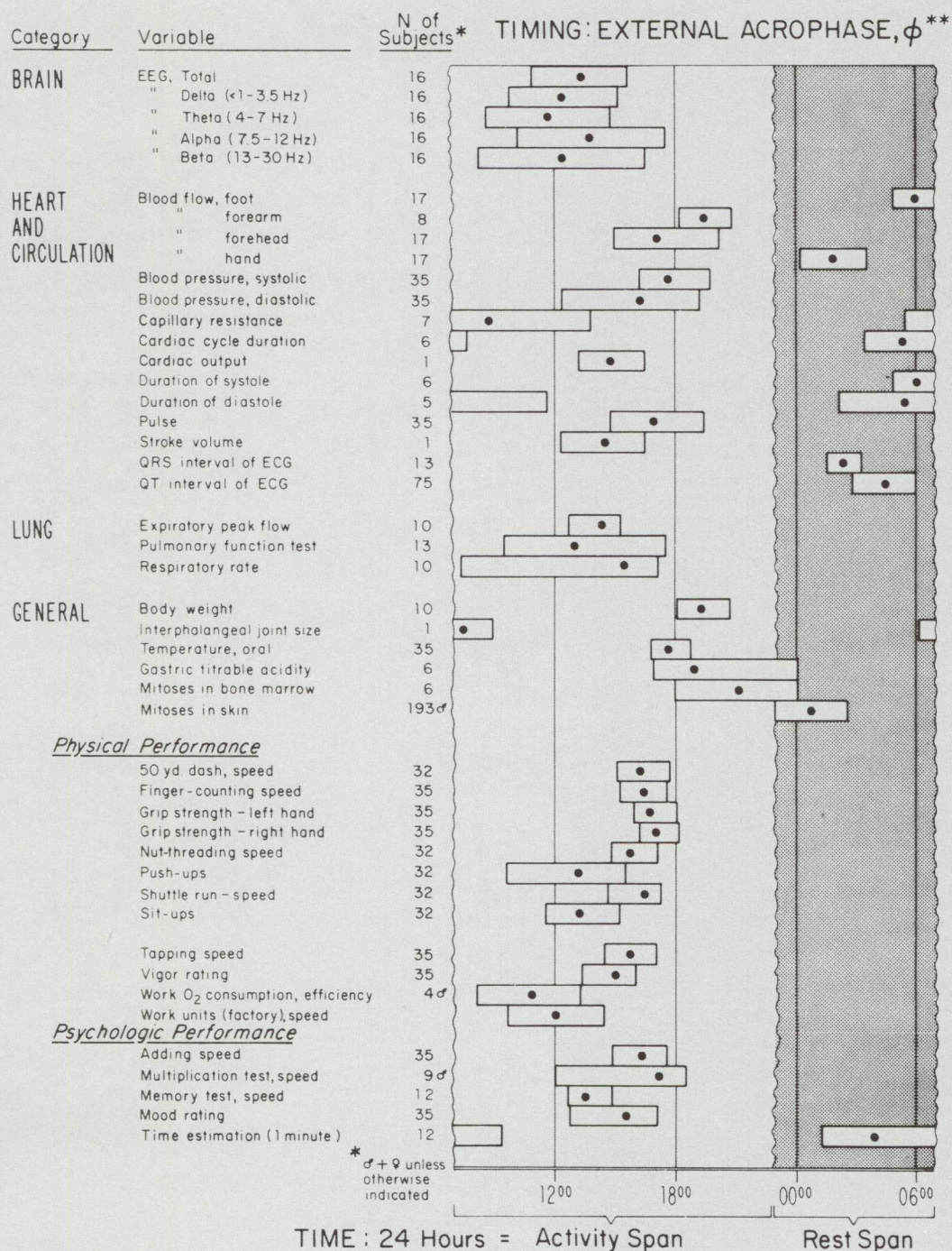
In this case, says Lakatua, "the flatness of the rhythm reflects some abnormality. And if

DAILY PEAKS IN THE HUMAN SYSTEM

When's the best time to add up the checkbook? After 3:00 in the afternoon, but before dinner. When will a shaving cut heal most rapidly? After 11:00 at night. As this figure shows, peak periods of physiological activity and physical performance vary predictably throughout a 24-hour day.

The graph, a statistical composite of data from many volunteers, shows when most people hit peak performance most of the time. But as we all know, some people, such as early risers or night owls, have marked individual differences in peak activity times.

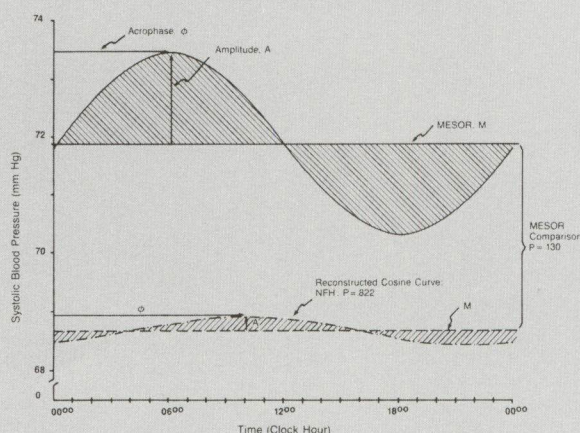




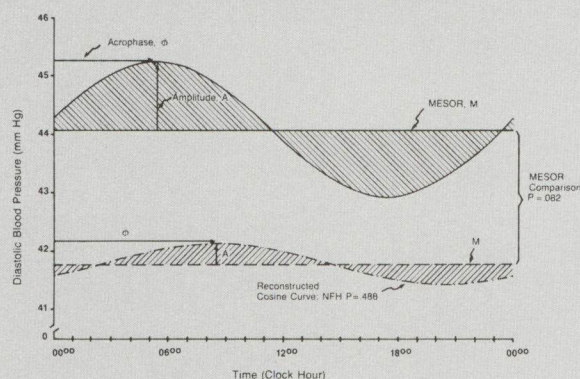
** Cosinor approximation of high values in circadian rhythm. Dots = acrophases; bars = 95 % confidence limits. Non-overlapping bars indicate statistically significant differences in timing

DAILY BLOOD PRESSURE CHANGES IN NEWBORN BABIES

CIRCADIAN VARIATION OF SYSTOLIC BLOOD PRESSURE (SBP) IN 23 NEONATES WITH A NEGATIVE (NFH) & 30 WITH A POSITIVE (PFH) FAMILY HISTORY OF HIGH BLOOD PRESSURE



CIRCADIAN VARIATION OF DIASTOLIC BLOOD PRESSURE (DBP) IN 23 NEONATES WITH A NEGATIVE (NFH) & 30 WITH A POSITIVE (PFH) FAMILY HISTORY OF HIGH BLOOD PRESSURE



Circadian rhythms in blood pressure in newborn infants may predict the infants' risk of developing high blood pressure later in life. Here a graph of blood pressure measurements from 53 newborns shows that infants with a family history of high blood pressure have a markedly higher circadian amplitude than do newborns without a family history of hypertension. Studies like this can help identify infants who need preventive therapy.

we know that a woman has this pattern, we can create a low-risk pattern of hormone levels either by stimulating production of prolactin or by implanting a drug pump in high-risk people."

Another study, run on a woman who wore a specially designed bra to monitor breast temperature, showed that one breast underwent daily, weekly, and monthly temperature cycles. The other, which showed no such cycles, turned out to have a hidden cancer.

Technology: The Key to Applying Chronobiology to Medicine

As these studies show, trying to learn about chronobiology without sensors and computers would be a formidable task. Halberg believes that few people have the patience of Sanctorius, who not only lived on a balance for a time, but also collected a 30-year record of fluctuations in his weight.

Nevertheless, many chronobiologists have followed Sanctorius' tradition. In documenting biological rhythms, chronobiologists have tested themselves repeatedly. They have sampled their own blood to detect hourly, daily, weekly, and monthly changes. They have worn temperature sensors, blood pressure cuffs, and ECG monitors. They've monitored themselves awake and asleep.

In the laboratory, chronobiological studies can involve measurement regimes that

would daunt an athlete. One study Halberg cites involved administering drugs to large numbers of mice in a rhythmic pattern. The investigator had to inject 270 mice — at the rate of one every 40 seconds — every three hours for 48 hours. After one day of rest, he had to begin the series over again. Luckily, Halberg recalls, the researcher was an Olympic runner.

Today, new sensors and monitoring equipment make long-term measurements of such functions as cardiac rhythm, body temperature, motor activity, and blood pressure not only possible but easy. But, Halberg stresses, “One should be able to say more than ‘we have found a rhythm here.’ ”

Scientists need to be able to identify some of the characteristics of the rhythmic changes, quantify them, and subject them to statistical analysis. The approach calls for sensor-based monitors teamed with computers. These allow researchers to look at a body function, take data over several days, and generalize the information to construct a single idealized day. Further analysis gives investigators an estimate of the variability associated with a rhythm and its characteristics. As Halberg points out, there’s an interdependency between chronobiology and technology.

Technology is also important when physicians want to use chronobiologic rhythms in delivering treatment.

“Chronobiology in drug therapy doesn’t just mean *when* to give drugs,” Hrushesky adds. “It also means that we have to consider the sequence of drugs we give and the intervals at which we give them. With programmable drug administration devices we can deliver drugs in the proper sequence and intervals

and at the proper circadian stage. Chemotherapy of this kind was impossible before these devices were developed.”

Ideally, researchers would like to identify several stable marker rhythms, such as body temperature, heart rate, breathing, or activity, monitor them automatically, and use them to synchronize drug delivery. Right now, for example, Hrushesky and his colleagues know that it’s best to give the anticancer drug cisplatin when a patient’s potassium excretion is highest. “But that’s a problem,” Hrushesky explains, “because we have to take and analyze a urine sample every few hours. The process is costly in both labor and time.”

Physicians who want to use chronobiologic therapy are looking for cost-effective sensors that can monitor marker rhythms. Ideally, these would allow a drug delivery device to follow a patient’s marker rhythms and deliver drugs, such as insulin, exactly when they are needed.

Researchers believe that the future of chronobiology in medicine lies with advances in technology. With the help of monitors, drug administration devices, and computers, doctors will be able to obtain an individualized assessment of health and prescribe individualized prescriptions for treatment for each patient.

“When computers and inferential statistics become ubiquitous,” Halberg asserts, “we’ll be able to exploit the significance of physiological changes fully and systematically in the clinic.”

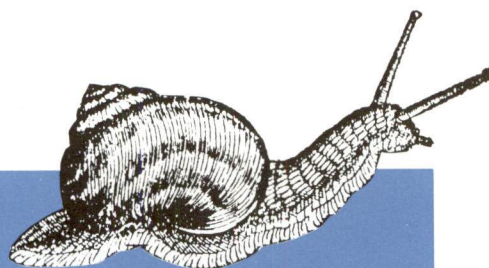
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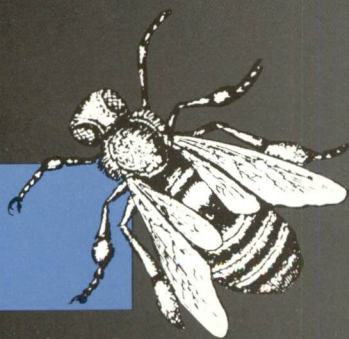
Major Contributors:

Dr. Franz Halberg
Dr. Franklin Barnwell
Dr. William Hrushesky
Dr. David Lakatua

Writing:

Barbara Scott Murdock
Director of Science & Medical Writing
Pine and Mundale Inc.





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OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

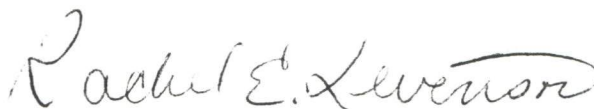
May 31, 1991

Dear Dr. Halberg:

Thank you for your interesting letter on chronobiology. Biologic rhythms are certainly a fact of life. How effective their analysis and modulation might be in promoting better health is worthy of careful study.

As I am sure you must be aware, the President's schedule is a very full one, indeed, and could not accommodate such a presentation as you propose. Might I suggest instead that you approach Assistant Secretary for Health James Mason as it is his office which bears principal responsibility for health promotion programs.

Sincerely yours,

A handwritten signature in cursive script that reads "Rachel E. Levinson".

Rachel E. Levinson
Assistant Director for Life Sciences

cc: Dr. Bakken

Dr. Frank Halberg
Director
Chronobiology Laboratories
University of Minnesota
420 Washington Avenue, S.E.
Minneapolis, Minnesota 55455

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Sincerely yours,



Rachel E. Levinson
Assistant Director for Life Sciences

cc: Dr. Halberg

Dr. Earl Bakken
Chairman, Advisory Board
Chronobiology Laboratories
University of Minnesota
420 Washington Avenue, S.E.
Minneapolis, Minnesota 55455

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9121516

FROM: HALBERG, Franz & BAKKEN, Earl; Chronobiology Labs, Univ of Minn

TO: DAB

DATE OF
CORRESPONDENCE: 05/20/91

SUBJECT: Request to Present Case to President Bush & DAB for
Funding for Study of Chronome.

ASSIGNED TO: Rachel Levinson

ACTION REQUIRED: Direct Reply

SENDER'S DUE DATE: OSTP DUE DATE: 06/10/91

DATE COMPLETED: 05/31/91

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CONTACT PERSON:

REMARKS: Damar changed the action on this from Bromley signature to
Direct Reply on 05/30/91.

DATE RECEIVED: 05/28/91
DATE RECEIVED DLS: 05/28/91

FILE: DLS