Chronobiotechnology and Chronobiological Engineering

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Chronobiotechnology and Chronobiological Engineering

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PREFACE

High blood pressure (BP) (with fats and smoking) is one of the three roots of cardio-cerebro-renovascular disease affecting up to 25% of the adult population. Hence, high blood pressure should be recognized and treated, to reduce any complications and prolong life, as noted by Michael Weber of the Veterans Administration Hospital in Long Beach, California. He further emphasizes the need for monitoring before one starts the treatment of high blood pressure. Indeed, he refers to the results of the Australian study on mild hypertension with a large percentage of placebo-responders and rightly suggests that many people are treated who should not be because of 'white-coat-associated high blood pressure'. He also points to the lack of standardization of techniques for data analysis and of methods of BP measurement. Ambulatory monitoring under usual conditions without concomitant recording of events does not allow even a qualitative assessment of the impact of varying stimuli, in Weber's opinion.

Paolo Scarpelli of the University of Florence proposes several clinical applications of automatic monitoring, namely in patients with malignant hypertension and in iatrogenous and hence reversible MESOR-hypertension. That automatic instrumentation is highly desirable for young children is another point of the presentation by Scarpelli. He documents the difficulty in obtaining reliable measurements on 9-year-olds. Such lack of reliability notwithstanding, he can, by the use of rhythmometric methods, find differences in the dynamics of BP variability between groups of 9-year-olds who have or do not have a family history of high blood pressure. Scarpelli presents such evidence to advocate that instrumentation yet to be engineered should eventually allow every child to be reliably and automatically monitored, with event recorders and soft-ware for rhythm analysis.

The contribution to this volume of the perinatologist Paul Meis is a logical next step in extending the need for monitoring instrumentation to the neonatal unit, as well as to pregnancy. Automatic neonatal blood pressure monitoring instrumentation is provided by Nippon Colin Ltd. (Komaki, Japan). With its use, inter-cardiovascular risk group differences are detected, but hardware for any chronobioengineering is not enough in itself. Additional ingredients are needed: the realization that we are dealing with dynamic functions that have predictable since rhythmic elements, Table 1, and that concepts that result in data reduction to the mean and a standard deviation are not invariably sufficient to exploit the information from chronobioengineering. Figure 1 shows the dynamic indices that have already proved of some value, as a first step in dealing with the dynamics of body function.

That one must pay attention to the waveform, be it by signal averaging or by harmonic analysis, is a point made by the overviewer of the sessions on blood pressure, Germaine Cornelissen of the University of Minnesota Chronobiology Laboratories. She has fitted 95 harmonics to each of 80 24-h series sampled at 7.5-minute intervals and has found prominent harmonics among the first 10. She suggests that the 11th to 95th harmonics represent mostly noise. She then documents that the amplitudes of the first 10 harmonics exceed those from the extrapolated noise characteristics, and suggests that these contribute most markedly to the circadian waveform. She emphasizes the availability of software for extracting information on dynamic endpoints. Her contribution strengthens Michael Weber's conclusion that although unsuccessful monitoring procedures still can occur, investigators and clinicians can now use the technique of ambulatory blood pressure monitoring with such a high level of confidence that they will generate usable data. That such non-invasive instrumentation is now available is a contribution of another of the authors in this volume, Verlin McCall of Irvine, California. He introduced the Pressurometer III, an important research tool, and tested it, with his brother Willifred McCall, a physician in everyday practice, where ambulatroy blood pressure monitoring belongs. Because of its weight and the need to put on electrodes, however, the Pressurometer is not the ideal instrument for long-term monitoring in the home.

Table 1

Dynamic endpoints complement static ones

STATIC		1. Mean, M:	casual systematic (e.g., MESOR: midline-estimating statistic of rhythm)
DYNAMIC	GLOBAL	2. Range, R:	total partial, e.g., 90%
		3. Standard deviation, SD	
	CHRONOBIOLOGIC	4. Trends:	a) Coefficients of polynomial terms, e.g., circadian mean (MESOR), M slope of linear trend
		5. Periodicities:	b) Rhythms, e.g., circadian amplitude, A circadian acrophase, ø circadian waveform (A,ø) of harmonics
	CHAOS	6. Noise:	white colored filtered (white or colored) noise
DEVIANT		7. Excess:	short-term-extent, timing; long-term-projection
		8. Deficit:	short-term-extent; timing; long-term-projection

The machine produced by Instruments for Cardiac Research (Liverpool, New York; a subsidiary of Squibb) has the unquestionable merit that it requires no electrodes. It does not have a rechargable battery and is by no means light in weight. It replicates the human observer in that it exhibites digit preference, an imprefection that will eventually be remedied.

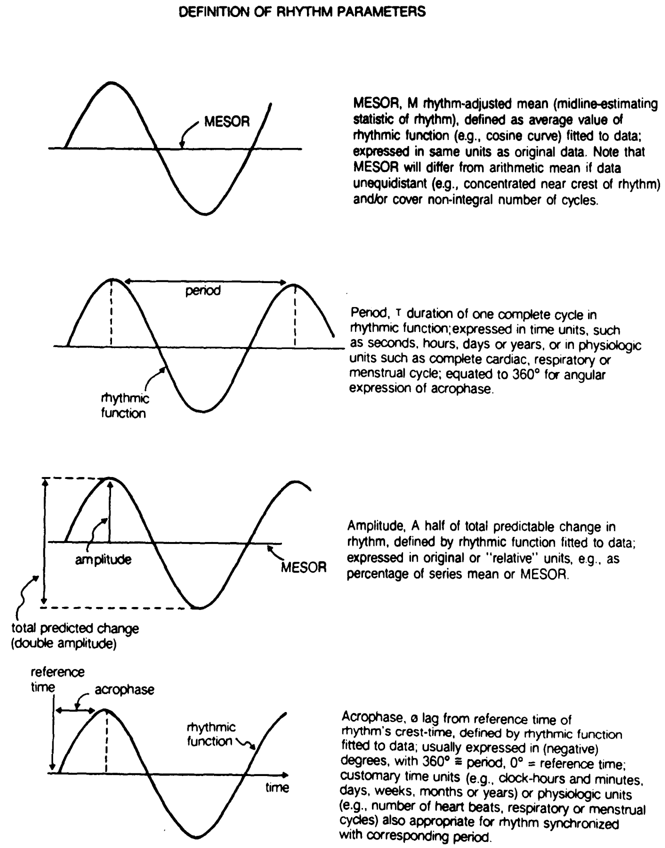


Figure 1: Definitions (for more detail, see Glossary of chronobiology, Chronobiologia 4, Suppl. 1: 189 pp.).

Lighter instruments are needed, and they are being produced. Room-restricted instrumentation, which can be carried with a handle but is too heavy to be worn, constitutes another need; the front-runner in this field is a machine manufactured by Nippon Colin (Komaki, Japan). This machine is used extensively in research by a number of chronobiologists in conjunction with software for rhythmometry that has to complement this machine and the fully ambulatory ones. Such progress notwithstanding, however, and with exceptions as noted above, in the view of most participants, the chronoengineering for software in dealing with the variability of blood pressure is the most urgently needed item.

For the pessimists among us, instrumentation available today provides no more than a choice between the proverbial devil and the deep blue sea. As to devils, first study Table 2. At first it appears that machines qualifying for this label are those encountered in public places that compute 'good days' and 'bad days' once one's birthday is indicated and some money inserted. Everybody knows (we hope!) that these machines are a put-on and have no basis in published scientific fact. All in all, the birthday-determined biorhythm machines are innocuous; of course, it has nothing to do with hardware and software engineering for rhythm assessment.

There are, however, also machines in public places that are clearly dangerous; they measure a single blood pressure or heart rate, as do individuals at health fairs (conventions of buyers and sellers of health information), often with a 'free' blood pressure included. Any single measurement may unduly alarm a person who is in the best of health. For instance, one may have been running to catch a plane. The plane's departure delayed, one finds time, at the airport, to take his blood pressure. This reading will be unduly high, if for no other reason than apprehension. Another person may be lulled into a false sense of safety by a single acceptable reading. Indeed, the danger of both false positive and false negative diagnoses looms large, in view of the variability of blood pressure shown in Figure 2. The time has come to do something about the fact that a single measurement of blood pressure, heart rate or a single value of many other functions must not serve as the sole basis for decisions regarding health when, in clinically healthy men, systolic and diastolic blood pressure vary within 24 hours, on the average by 69 and 56 mm Hg, respectively.

The presentations at the session on electrocardiographic monitoring emphasize the need for instruments that record for durations longer than 24 hours. This need can be shown in two ways. A first pertinent fact, from the viewpoint of classical cardiology, is that of 12 monitoring days, one day may be devoid of any and all ECG-recorded ischemia, whereas on subsequent days, there is consistently ECG evidence for ischemic attacks (Biagini et al., 1981). What is even more interesting, a pattern of ischemia can be the expression of several rhythms with different frequencies. In the case of Biagini et al. (1981), two components are actually phase-drifting circadians, each with a

Table 2

PUT-ONS:
ONE OF THEM DANGEROUS

Machines:

Sell you information on:
1) Birthday biorhythms:
Your "good" and "bad" days

2) Health measures:
Your blood pressure and pulse

Results:

1) Your "good" or "bad" days may not be true at all

2) Your physiologic measures are true only for a moment (whether or not influenced by your arm size or the machine's operating condition)

Action

If you judge your health by single physiologic measures, this is the dangerous put-on

Alternative:
Chronobiology

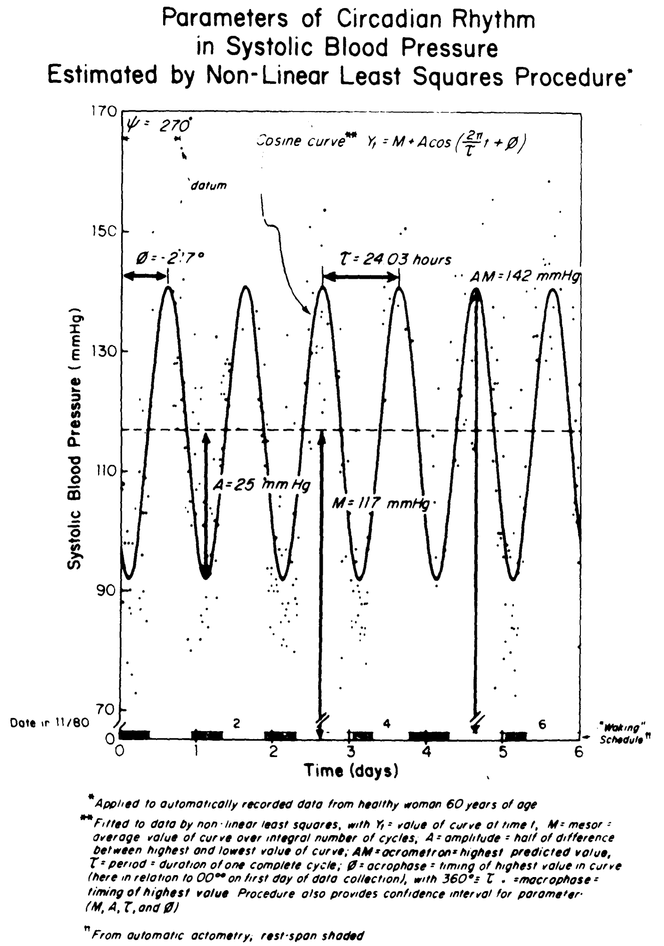
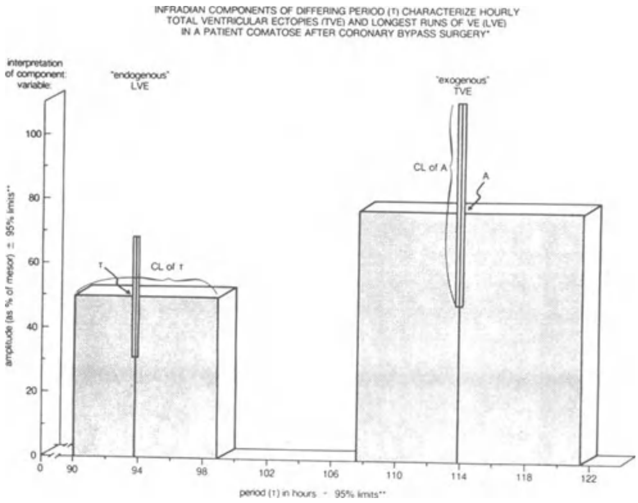


Figure 2: Physiologic variability can be rendered predictable and such predictability can be exploited when other approaches fail (Chronobiologia 8: 351-366, 1981; Postgrad. Med. 79: 44-46, 1986).

confidence interval for the period that does not cover precisely 24 hours (Halberg, this volume). It then becomes a rhetorical questions whether a 24-h ECG sufficies as a representative record. An analogy might be considered to further emphasize the limitations of 24-hour records for circadian and infradian studies. One-day monitoring of a circadian rhythm (in any variable) is equivalent to taking the pulse by monitoring for a duration corresponding to the average time of a single heartbeat. During, say, a second of monitoring, one may not pick up a single beat. To drive this analogy to the absurd, one may have to conclude that the patient has no heartbeat.

Figure 3, a summary of data collected by Charles Leach, another symposium participant, provides yet another reason for the need to construct recorders that monitor for spans exceeding one day. The periodicity observed by him is an infradian one; just as one wouldn't wish to monitor a circadian rhythm during an 8-hour span, one shouldn't limit monitoring to a single day to characterize a rhythm with a period of several days.

Ivan Bourgeois of Medtronic BV in Kerkrade, Holland, the chairperson of the cardiology session, considered the indications and specifications for a chronobiologic pacing of the human heart. His firm, Medtronic, has already introduced pacemakers guided by instantaneous motor or respiratory activity. With him, one can emphasize the need for pacing not only in the light of instantaneous demands, but anticipatory changes in pacing may have value. A programmable pacemaker with a built-in recorder and physiologic laboratory could take into account the rhythm structure of pathology.



<u>Figure 3</u>: The presence of rhythms with periods of 3.5 days or even longer periods makes it mandatory at the outset to monitor the electrocardiogram for spans exceeding 24 hours (Chronobiologia 10: 138, 1983).

What applies for electrical treatment in theory has already been applied to drug administration devices. The most advanced system was presented by Robert E. Fischell of the Johns Hopkins University Applied Physics Laboratory. He has devised a microprocessor-controlled implantable, externally programmable medication system aimed particulary at the release of insulin into the human body. The system equals a fully implantable, programmable infusion pump consisting of a patient's programming unit, a medication programming unit, and a medication injection unit. The infusion pump is refilled at intervals of several months; it serves as an artificial pancreas.

This latter topic is succinctly discussed, on the basis of extensive experience, by the president of the University of Montpellier and chairperson of the session on pumps, Jacques Mirouze. Pumps used by him already assure a minimal uninterrupted insulin supply (around 1 unit/hr) and are adjustable so that more insulin is delivered with meals and physical exercise. As noted for the pacemaker and as applies to the pump as well, a proper program will anticipate spontaneous rhythmic changes in demand and will provide for rhythm-stage-dependent responses to meals. A contribution to this volume by Yves Lazorthes and Jean-Claude Verdier of the University of Toulouse, France, considers automatic drug administration devices and their mechanisms, as well as their application in treating cancer pain, spasticity or malignant brain tumors themselves. Anthony F. Yapel and Felix Theeuwes, of 3M and Alza Corps., respectively, introduce their technologies applicable to chronotherapy. 3M already offers a product line of volumetric external infusion pumps and Alza's mini-osmotic pump is extensively used in experimental research. With the Medtronic implantable externally programmable pump, Marco Cavallini, now of the University of Rome, documents, for the first time in a middle-sized animal (beagle), a clear gain from the use of sinusoidal schedules originally introduced in Minnesota for treatment with ara-C, and now extended by him for treatment with cyclosporine.

Another highlight of the meeting was the session on data acquisition and analysis sytems. Its chairperson, Martin Knapp of the University of Nottingham, England, was responsible for introducing a clinical system involving computers for bedside monitoring, e.g., after a transplantation. In this session, Ramon C. Hermida of the University of Madrid made the point that indices such as the rhythm parameters defined in Figure 1 may well be used as such, but that chronobiologic methodology includes, in addition, a wealth of other methods. From the viewpoint of chronobioengineering, sooner or later, the software of today should become the hardware of tomorrow. For the storage of chronobiologic data, Robert M. Goodman of the Franklin Institute (Philadelphia, Pennsylvania) presents a device that allows large scale data acquisition and storage. Salvatore Romano of the University of Florence shows the need for using multiple methods to check on results. In this context, he provides an independent confirmation of the finding on 9-year-olds that the dynamics (rather than the static mean) separate groups of children with or without a family history of high blood pressure.

Jean De Prins of the Free University of Brussels reviews the problems associated with actual data collection and shows that "noise" originates in different ways. He distinguishes different noise types, including fluctuations of the biological system itself, flutucations external to the organism monitored yet measured by the transducer and noise originating from both the transducer and the sampling device. This noise may be redistributed over the frequency range investigated (aliasing). De Prins reemphasizes that mathematical theories rely on simplifying assumptions (such as normality, independence of errors, stationarity and erogodicity) that are not necessarily verified in practice. Accordingly, he concludes that in view of different experimental conditions, an array of methods of analysis has to be considered, each with its own domain of applicability.

The Table of Contents lists many internationally known contributors to this volume. The major point may well be that the challenge of chronobiologic engineering should take us, in everyday medical practice and in self-help for health care, to wedding chronobiologic software to the hardware. This critical step would allow a fuller exploitation of data collected with classical tools, such as thermometers and sphygmomanoneters, and of those obtained with automatic recorders, which should sooner or later be provided not only with solid-state memories but also with proper analyzers. The Cardiff symposium volume, if it did no more, assembles hard data to document the need for both software and hardware engineering, so that the predictable and rhythmic dynamics, that are the web of all life, can be properly assessed.

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Franz Halberg

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Our hosts in Cardiff, Wales, Drs. Keith Griffiths and Douglas W. Wilson and their staffs from the Tenovus Institute for Cancer Research left no stone unturned to make sure that we were subjected to hospitality of the highest quality and at the lowest possible cost. Douglas Wilson was attentive to every detail before, during and after the meeting. The following companies also made significant and much appreciated contributions to the development and support of this program:

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Opening Remarks: RATIONALE AND GOALS OF THIS WORKSHOP

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A well-attended NATO-sponsored Advanced Study Institute was held in Hannover, Federal Republic of Germany, from 13-25 July 1979. The subject title of that school was "Chronobiology: Principles and Applications to Shifts in Schedules". The proceedings, edited by L.E. Scheving and F. Halberg were published by Sijthoff and Noordhoff in 1980. It was a two-week course which dealt with the broad subject of chronobiology, but it tended to focus on the practical problems of shiftwork and of transmeridian travel (jet-lag). We believe that this tutorial course had impact. A number of the faculty and students who attended are now among the leaders working on, or heading up projects on, shiftwork and jet-lag throughout the world. Thus, the institute helped to intensify worldwide lay interest in problems of shiftwork and the associated changes in internal time structure.

An emergent consensus from the 1979 NATO school was that although the state-of-the-art of laboratory-based measurements of circadian function had reached a high level of sophistication and practicality, this clearly was not the case for our capacity to measure rhythms with several frequencies on vital human functions in the field.

In everyday life, many rhythms are extremely noisy. Although such rhythms have been measured and certain components of them became clearly evident, measurements done by the subjects themselves or by staff are cumbersome and time consuming, and they interfere with the work itself. Thus there arises an uncertainty as to how much self-measurement is tolerable and when automatic-measurement becomes mandatory. Self-measurements are useful and indispensible for certain purposes and conditions. They cannot readily serve, however, for the assessment of certain ultradian rhythms with very high frequencies which we now know interact with circadian rhythms. Moreover, in a variety of conditions, the rhythms in self-measured or automatically obtained data are still covert and are revealed only by special methods of analysis.

A major task for the chronobiologist of the future is to resolve better the temporal structure of man as well as the experimental animal. To do this he will need reliable, socially acceptable instrumentation that is comfortable to use over long spans of time. But this is not enough. There is also an urgent need to be able to analyze in a meaningful, understandable way, the data collected as one goes; thus rapid reduction of data is essential.

With the above as a background, the organizers saw the need for a workshop that would deal specifically with what kinds of continuous monitoring devices are available, how they can be improved, and how are the data handled once they are collected? Our overall objective in planning was to bring together, from industry, government and the university, some of the world's leadership in this area. We decided that the fields to be covered would include the monitoring of body core and surface temperatures, gross body movement, psychophysiological performance (with special emphasis on the nervous system), circulation and respiration, as well as vigilance, visual acuity, cognitive functions, reaction time and well being. Also of great concern was how to improve chronobiologically patient monitoring; treatment devices, such as cardiac pacemakers; and drug-administration systems, such as pumps and oral and transdermal systems. Further within the scope of the meeting was the collection of biophysical, biochemical, and numerical analyses of blood, urine, sweat, and saliva in both the human and experimental animal.

A major fundamental rhythmic variable measured in the past has been body temperature, and this will be the subject of the first panel. From this panel of 11 top experts from around the world we should learn first, from the reviewer the historical development of instrumentation, why is body temperature an important variable to monitor, the problems encountered, and the state-of-the-art of the instrumentation used to measure temperature. What are the problems for the subject who must wear such instruments over long spans of time in contrast to wearing them over short spans of time.

Most important there should emerge from this panel, as from every other panel, recommendations as to how technology might be improved to resolve better the whole spectrum of rhythmic frequencies characterizing this fundamental rhythmic variable. I am pleased to say that a new technology for monitoring deep body temperature through microwave sensors has emerged; and the developer of that technology D. V. Land of Glasgow is on hand to explain what I believe will become the "wave-of-the-future" for obtaining clinically valuable information about internal temperature variation. The technique is passive, non-invasive, and completely safe. The publication that follows this workshop should serve as an up-to-date reference for anyone interested in this particular subject.

The second panel will deal first with the monitoring of motor activity and the electromyogram: Of what practical use are the data obtained from the actograph? The reviewer should tell us why it is important to monitor motor activity, the historical development of such monitoring equipment, and the state-of-the-art of the present equipment; he has played a major role in bringing about the latest technology. Most important we want to know its limitations as well as how such monitoring can be improved and how one handles the large amount of data obtained? Following this, we will hear about the more up-to-date ways now available for monitoring vigilance and psychological endpoints. We know that in the past many of these measurements depended on pencil and paper tests; but now more sophisicated techniques have been developed, and we would expect to learn from this group what is desirable for advancement in the future.

The final afternoon panel will deal with monitoring of eye movements, respiration, and electroencephalogram recordings, and their importance and reliability in health as well as sleep. We should learn whether the instrumentation available today is adequate for long term measurement or monitoring of the EMG, EOG, and the EEG directly and simultaneously. Do the instruments available reliably differentiate dream (REM) sleep from non-dream sleep? For example, are the instruments that give an analog recording of the parameters of sleep as good as those that give us direct recordings of EMG activity, eye movements or EEG activity? Can the instruments at hand differentiate a true from an artifact signal and can the intrepreter distinguish one from the other or does he have no idea as to which is which? Can you believe summary data?

Tomorrow morning we deal with monitoring of blood pressure, a subject that has been a great interest to me. It has been widely documented for blood pressure that self-measurement can complement measurements by medical or paramedical staff. We now know that developments in instrumentation, the use of automatic blood-pressure monitors, complements (rather than replaces) the conventional sphygmomanometer. What the automatic instrument does is to provide more refined cardiovascular profiles which are necessary to better resolve and therefore to better understand changes in blood pressure. We have arrived at a stage where most clinicians accept the fact that blood pressure, especially in the hypertensive, shows a remarkably circadian rhythm. But, it also is a variable that is characterized by many other frequencies including weekly or circaseptan rhythms.

The blood-pressure panel will be followed by a group dealing with chronobiological electrocardiographic monitoring; and from this panel we should learn what are the chronobiological implications of screening, diagnosis, and, most important, treatment. What is the state-of-the-art of instrumentation; what is needed for advancement?

Since the biological time structure is continually changing, we know that any response to a drug or any other agent will vary. The experimental evidence is overwhelming that the timing of drugs according to the body rhythms can bring about a therapeutic advantage. This is especially important in the timing of cancer chemotherapeutic agents, but it also is important to a diabetic patient receiving insulin as well as in the regulation of blood coagulation. Can the physician afford to ignore this variation in susceptibility to various types of medication? This indeed is a very important panel and those involved are pioneers in this endeavor. The current practice of medicine largely disregards timing of drug administration. The development of extra- corporal programmable drug-delivery systems will make clinical "chronotherapy" both possible and economical. Science and technology must come to grips with the best way to administer drugs chronobiologically. There is a great potential in this field, both for industry, and, more importantly, for the health of man.

There are problems associated with clinical laboratory instrumentation; this is a difficult area because it usually involves the monitoring of biochemical variables, but it is an area that we must address in the future. Overviewing this session is a very competent clinician and laboratory specialist. The same problems pertain to laboratory monitoring of the temporal structure of animals and plants, and again we are fortunate in having an exceptional panel of experts.

Finally the panel on data acquisition and analysis systems on the morning of the last day has an important task before it. It is essential to continue to develop better tools for automatic data collection and transfer, as well as for transient and definitive data-base storage. Any information gained from a given subject should be analyzed as it is collected, for the purposes of monitoring, yet it should also be accumulated for the derivation of individualized reference values for that subject to assist in decision-making. It is extremely important that data obtained are meaningful to the referring physician and also compatible with a computerized medicine information system. The stored data can also form part of a data base for the construction of peer-group reference values and for even broader research purposes.

Since storage and analytical capabilities are limited, it becomes essential that the variables that we do select to study are important in performance as well as systemic functions such as core temperature, cardiovascular indices, performance vigilance, and automatically monitored body chemistry; such variables will have to be compared for their relative merits. Only then will it be possible to investigate and eventually optimize those factors that underlie a given worker's ability to perform mentally and physically.

We should also develop answers for those who continually ask the questions: How do we measure? How do we schedule? Or more generally, how do we use chronobiology in industrial hygiene as well as in preventive medicine. Of central importance is the question of relevant functions and sample design. If we can record only a limited number of variables from a subject: 1) Which ones are essential and which are non-essential, redundant, or of less importance? There is already general agreement that core temperature and motor activity measurements are high on the list of essentials, 2) What rank is given to respiratory, circulatory, and neural-system parameters? 3) When do we wish to extract simultaneously from our subjects some measures of vigilance, visual acuity, cognitive functions, and sense of well-being? 4) What priorty do we give the collection of blood, urine, breath, sweat, and saliva samples? 5) What are the practical limitations in terms of sampling frequency and duration? (6) What kinds of sensors and collecting devices are presently available, and are they sufficient to the task? 7) What kinds of interpretive techniques are presently available (inferential statistical graphic, beyond doubly plotting, etc.), are they sufficient to the task, and what changes are needed? and 8) What kinds of interventions, strategies to effect mitigation, are available, are they sufficient to the task, and what changes do we need?

Each of the above questions represents a problem for which we already have available some fairly reasonable, although not entirely satisfactory, answers. For each question, we ask our panels of experts to come up with some answers and to make suggestions for the future.

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