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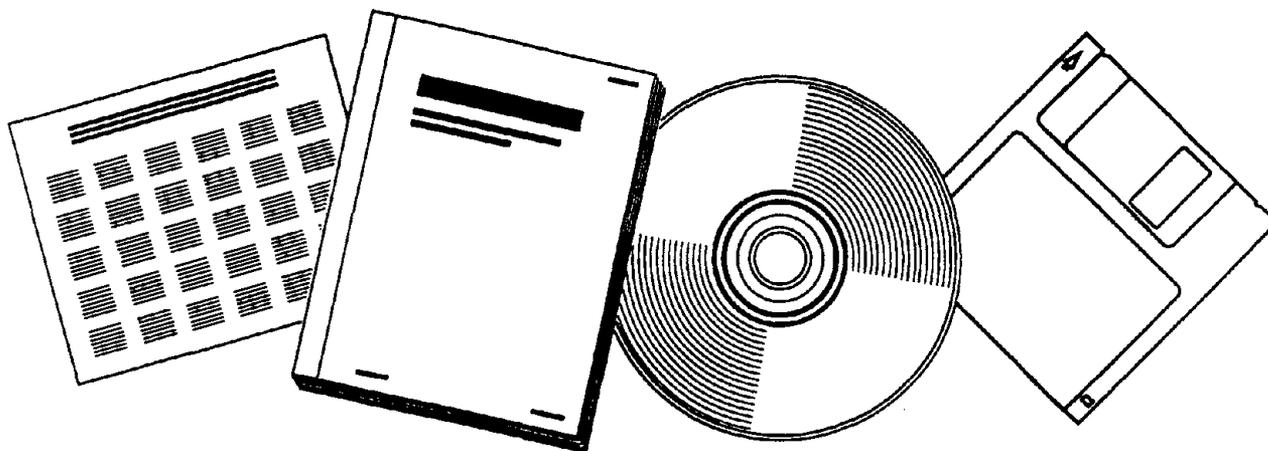
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## SHIFT WORK AND HEALTH-A SYMPOSIUM HELD AT CINCINNATI, OHIO ON JUNE 12 AND 13, 1975

NATIONAL INST FOR OCCUPATIONAL SAFETY AND HEALTH  
CINCINNATI, OHIO

JUL 76



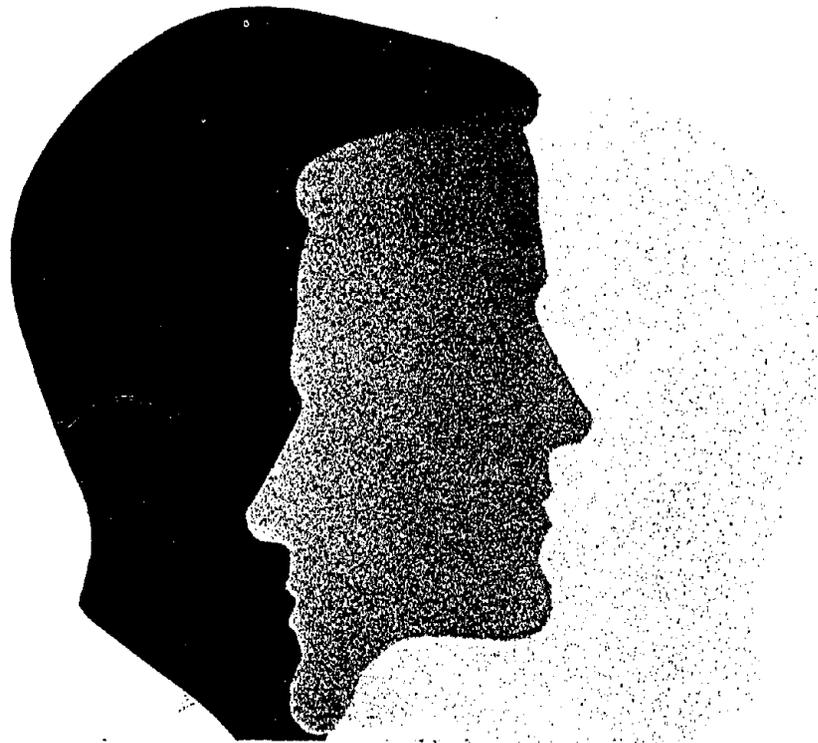
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# Shift Work and Health

.....a symposium



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**U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE**  
Public Health Service  
Center for Disease Control  
National Institute for Occupational Safety and Health



# **Shift Work and Health**

**A SYMPOSIUM**

**Sponsored By  
The National Institute for  
Occupational Safety and Health  
Held June 12 and 13, 1975  
Cincinnati, Ohio**

**U.S. DEPARTMENT OF HEALTH, EDUCATION,  
AND WELFARE  
Public Health Service  
Center for Disease Control  
National Institute for Occupational Safety and Health  
Office of Extramural Activities**

**July 1976**

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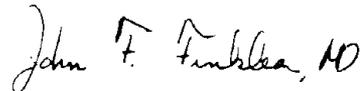
## FOREWORD

The National Institute for Occupational Safety and Health (NIOSH) is responsible for conducting investigations and research to assure a safe and healthful work place for the working men and women of this nation. In fulfilling this mandate, the Institute initiates and supports a variety of field studies and scientific research with the intent of establishing criteria for safe levels of exposure to occupational stresses.

Because available information with respect to whether adverse effects from changing work regimens can occur was inconclusive, NIOSH sponsored a two-day meeting to explore and identify directions and methods needed to conduct meaningful research on the relationship between shift work and worker health and well-being.

The goals of the meeting included arriving at an understanding of the social, psychological, and physical effects of existing systems and identifying optimum schedules to be recommended to industry to minimize recognized negative effects. Toward that end, issues such as circadian rhythm versus social adjustment research and the owl-lark phenomenon research were addressed.

These proceedings were developed from the meeting and are detailed in the hope that the findings presented will serve as the basis for future investigations into this important, but little known, area.



John F. Finklea, M.D.  
Director, National Institute for  
Occupational Safety and Health

## **PREFACE**

The papers presented herein were first prepared for oral delivery and have been edited as necessary for publication in this volume. Discussions prompted by each presentation are included immediately following the specific presentation.

Sponsorship of the symposium and publication of this volume by NIOSH do not imply that the Institute endorses the views expressed.

## ACKNOWLEDGMENTS

The editors wish to express their thanks and deep appreciation to all speakers, discussants, and invited guests.

We wish to acknowledge with gratitude Austin F. Henschel and Michael J. Colligan for their participation in the technical review of these proceedings, Denise M. Gerth and Joan E. Baugus for indispensable assistance in arranging and hosting the symposium, Alphonse F. Schaplowsky and Raymond C. Sinclair for effective audio-visual presentation and Russell L. Hinton and Richard A. Carlson for their separate professional contributions to the final document.

The manuscripts were diligently edited under contract by Tree House Associates.

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# **Opening Remarks**



**OPENING REMARKS**  
**and**  
**STATEMENT OF PURPOSE**

*P. G. Rentos*

It is with privilege and distinct pleasure that I open this two-day session and welcome all of you to our first symposium devoted to the topic of Shift Work and Health.

As I glanced over the program in preparation for these remarks, I suddenly became aware of the varied backgrounds of our speakers and guests who traveled many miles to attend and participate in the discussions to follow. Some of the professions and professional disciplines represented include: Bioengineering, Sociology, Medicine, Psychology, Pathology, Physiology, Safety, Neurology, Nutrition, Anatomy, Industrial Hygiene, Ergonomics, Psychiatry, Nursing, Economics and Toxicology.

This emphasizes an important fact: the problems of shift work are universal and cross disciplinary lines. Whether this signifies the complexity of the situation or, on the contrary, that we may already know so much that we are able to specialize, is not clear. What is clear, however, is that the questions being asked are becoming more frequent and the answers harder and harder to come by.

It is hoped that the technical papers to be presented here today and the group sessions tomorrow will increase our understanding of this all-important area and will place us well on the road to providing criteria essential to the establishment of standards that are both effective and realistic so as to ensure that those engaged in shift work can do so without threat to life or well-being.

You may have wondered why the Office of Extramural Activities, which functions primarily in grants, has an interest in all of this. We see it as an extension of our grants programming effort. We feel that if we can create a forum where researchers in occupational safety and health can come together to present their research methodologies and findings and avail themselves of open and informal discussion of related work conducted by others — both within and outside of the Institute — our fiscal appropriations are better spent.

Let me emphasize that the format of our meeting is to be informal; and we will expect that the research topics will vary from the most basic to the very practical and applied. We hope that there will evolve a feeling for how even the most fundamental research can be designed for the long-range goal of ultimate application for worker protection.

At the same time, those of us who are responsible for program direction or implementation or for the development of criteria for standards will, hopefully, walk away with a better understanding of the issues and be better prepared to deal with them in a more frank and rational manner.

Our moderator for these sessions is a gentleman who has worked hard to insure their success. His technical handling of this difficult subject, in my opinion, is superb. It is my pleasure to introduce Dr. Robert Shepard.

## **OPENING REMARKS**

### **From the Moderator**

*Robert D. Shepard*

I had prepared a number of remarks, but, because we're behind time and Dr. Rentos has covered basically the same ground that I had planned to cover, I'll say just a few brief words.

On behalf of the stress research section of the Behavioral and Motivational Factors Branch, I should like to welcome our distinguished guests, speakers, discussants and attendees.

The program was organized on the presumption that there are significant health and safety consequences to shift work. However, the research in the field remains inconclusive. Much of the evidence for health consequences points to psychological and behavioral factors as directly involved in, if not the primary cause of, the reported health consequences. Thus, the strong involvement of our section in this program.

Our task in the next few days is to focus on the following:

- (1) Is shift work a significant health and safety problem?
- (2) How can we best do research to evaluate this, further eliminating the factors that have confounded much prior research?

To provide a broader perspective of the government organizations supporting this endeavor, I am pleased to present Dr. Austin Henschel, NIOSH, and Mr. Robert Mahon, DOL-NIOSH Liaison, who will give brief introductions to the overall perspective on which this symposium has been organized.

## NIOSH POINT OF VIEW

*Austin Henschel*

The objective of the 1970 OSHA Act was to insure that the work environment contained nothing that would constitute a threat to the health or the safety of the worker. This act also established the National Institute for Occupational Safety and Health, and charged it with the responsibility for determining whether there was anything in the work environment or, if one looks a little broader, in the work practices which would endanger the health of the worker.

This charge has led NIOSH to investigate a vast variety of occupational situations and occupational stresses and, on the basis of the studies, to establish the criteria for safe limits of exposure to occupational hazards.

As a result of some of the recent scientific findings that have appeared in the literature on biorhythms, we believe it must be determined whether shift work and changing shift schedules in themselves may constitute a primary stress which would affect the health and safety of the worker, or that they may be secondary factors which would in themselves alter the capabilities of the worker to handle stresses of other kinds whether they were chemical, physical, or climatic stresses. In either case, if shift work were a primary hazard or secondarily altered the capabilities of the individual to handle other primary hazards, it would be extremely important to the NIOSH mission to insure a healthful work environment.

Shift work, of course, is not new. Around 1860, there was concern expressed over bakers who always worked at night and some effort at that time was made to try to regulate the work hours and the conditions under which bakers worked. Little came of it, but interest in the effects of night work was recognized at that time.

Many of the manufacturing processes today are such that continuous operations are required. The operations must be continued throughout the 24 hours and for seven days a week. This has made shift work a fact of life.

Man is basically, either by our many years of habits or genetically, a daylight-oriented animal. We function best in the daylight; at night our functions are at a minimum.

Now, with the advance of good lighting systems, of course, we can change this whole system. We can make it light for the man any time of the day or night it is necessary for him to operate. We are able and do impose upon the worker a different type of light-dark system. Does this have any effect on the worker, upon his capabilities, longevity, mortality, morbidity experiences or his well being? This knowledge is necessary for determining whether there is an occupational health problem.

The second bit of information we need is, if there is a problem, how big is it? How many people work at night or are on shift work? There are few statistics on this in American industry or that show the percent of workers who, at some time during the year, are involved in shift work or shift schedules that require that they work either day, afternoon, or night shifts, alternating between them. One survey that was made outside America, indicated that approximately 20% of the workers were involved in shift operations. If 20% in our labor population is on shift work, this is a high number of workers. If it is only a few workers, the problem would be entirely different and the approach to the solution would be entirely different.

We need to know whether shift work is a problem, whether it is a primary or a secondary problem to worker health, and how many workers are involved.

Data are needed to establish criteria or guides for shift operations which would minimize the effects on the health or the safety of the workers.

## OSHA POINT OF VIEW

*Robert D. Mahon*

I bring you greetings from Alexander Reis, the Assistant Associate Secretary of Labor for OSHA, and his special assistant, Dr. Don Lassiter. They wish you a very successful and productive symposium.

When Dr. Rentos first approached me and asked if I felt that shift work impacted upon the worker's health and safety, I had to admit that I wasn't sure. Being somewhat of an applied researcher, I thought back over my own shift working experiences. I worked shifts at Swift and Company, before WW II, either on the 7 to 3; 3 to 11; or 11 to 7 shift. The shift work schedule was rotated each month. During WW II, while at sea on U.S. merchant ships, each crew member stood four hours on, eight hours off, depending on the watch he happened to have. When in port, he stood eight hours on, and 16 hours off. Since that time, I've been going to school or working. It seems as if I've been working 24 hours a day so shift work hasn't been a problem.

Even after talking to people with whom I've worked, both in the private sector and the public sector, I still have the same questions in my mind that Dr. Henschel just outlined for you.

However, I did some research prior to this seminar. I talked to people within OSHA about the problem or the apparent problem. I also talked to two men who happen to be corporate safety directors for companies that have a large number of employees doing shift work. I talked to Howard Rebholz, Rath Packing Company, and Bill Turney, Texas Instruments Company.

We discussed the broad subject areas that are to be covered in this symposium in a general sense. There were more questions raised than were answered. For instance, Bill Turney reported that there were no apparent significant changes with respect to the injury and illness rates of their employees doing shift work. Texas Instruments has experimented with the so-called "compressed work week," that is, three 12-hour days, and four 10-hour days. Although they didn't discern any significant changes in the employees' injury and illness rates, they did discover some of the shift workers exhibited more than normal sociological and psychological concerns. They also discovered that the employees' production

yields were adversely affected. So, with that background and my own personal experience plus what I've learned from the investigation of hundreds of accidents in industry over the last 30 years involving people doing shift work, I share Dr. Henschel's concern and the one that Dr. Shepard has outlined to you. We have a need for more information.

In conjunction with addressing this need, frequently asked question is: Where does NIOSH get the authority to look at this apparent problem? In your folders you have a copy of a green sheet labeled PL 91-596. This sheet lists on the left hand side the highlights of authority for the Department of Labor, and the top one reads: "to promulgate, modify, and improve mandatory occupational safety and health standards."

Now how do they go about doing that? In order to do it, they must keep in mind the objectives that are called out in the Occupational Safety and Health Act of 1970 and I'll reiterate what Dr. Henschel said, because he said it very succinctly, and I think it bears being kept in mind throughout this entire symposium: "To assure safe and healthful working conditions for working men and women."

If we skip a few lines, it goes on to say: "by providing for research, information, education, and training in the field of occupational safety and health and for other purposes." One of the high points of OSHA's objectives, then, is to gather the most authoritative and most current research information from NIOSH and other sources, so that when they promulgate a standard, it will be based on reliable data.

I trust that, as the result of the two days of meetings we are embarking on here this morning, there will be much data forthcoming that will be helpful to OSHA in fulfilling its obligation of providing a safe and healthful work place for the working men and women of the United States.



**Session I**  
**Formal Presentations**  
**and Discussions**



## SOME ASPECTS OF CHRONOBIOLOGY RELATING TO THE OPTIMIZATION OF SHIFT WORK

*Franz Halberg\**

I hope that these two days will show that the effects of shift work can be good, and bad, and indifferent. There are hard and fast data for making all three reports.

Our studies examine many different aspects of the question, such as:

1. Life-span and resistance after repeated schedule shifts.

Shifts in the timing along the 24-hour scale of a regimen of light (L) and darkness (D), alternating at 12-hour intervals ( $LD_{12:12}$ ) served to test any objective physiologic effects of repetitive changes in routine. Life span and resistance to toxic doses of Quabain were the variables examined in inbred mice kept under controlled conditions of temperature. Of course, we are not dealing with a direct simulation of either shift work or the aviators' schedule. No mental work on take-off and landing is imposed and the animal's own "spontaneous activity" is not intermittently impeded by immobilization in a cockpit or by the special requirements of other shift work.

The changes in schedule involve an abrupt institution of a  $180^\circ$ , i.e., 12-hour shift (when a 24-hour cycle is imposed, 24 hours thus are equated to  $360^\circ$ ). In human shift work a displacement by eight hours ( $120^\circ$ ) rather than by 12 hours often takes place and, more generally, displacements in schedule by less than 12 hours are common. However, the greater displacement of schedule ( $180^\circ$  rather than  $120^\circ$ ) may be desirable for tests of any effects from the maximum displacement possible on a 24-hour schedule in any one direction, i.e., as an advance or as a delay.

In two separate studies, a total of 370 female BALB/c mice about one year of age were studied. These animals were housed eight/cage in two separate but similar, if not identical, so-called rhythmometry rooms (Study A) or in special environmental chambers described elsewhere.<sup>59</sup> Female mice have, on the average, larger adrenals and higher corticoster-

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\*Co-authored by Dr. Walter Nelson, Department of Laboratory Medicine and Pathology, University of Minnesota at Minneapolis.

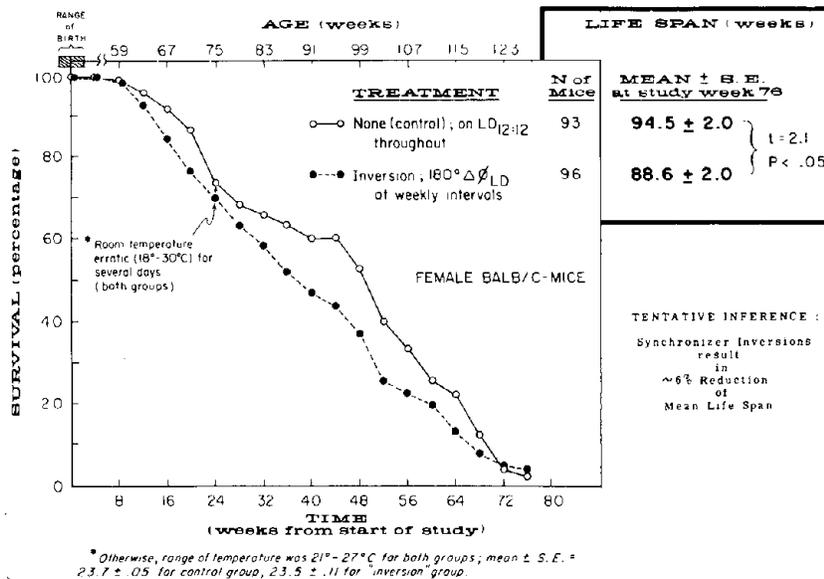


Figure 1. Survival of mice with and without exposure to weekly inversion (180°-shift) of daily lighting schedule (LD<sub>12:12</sub>), beginning at about one year of age.

one values in blood and adrenals.<sup>28</sup> Because of such hormonal sex differences and also because their sex-gland-related cycle is more readily defined than in males, they are preferred as experimental animals. Until proof is offered to the contrary, it is assumed that the use of female test animals does not restrict tentative extrapolations to both sexes.

Environmental temperature was kept at about 24°C. Food and water were continuously available. In each study, controls remained on a fixed LD<sub>12:12</sub> regimen throughout, while the LD<sub>12:12</sub> regimen of experimental animals was shifted weekly by 180°. The shift was instituted in alternation, one week by the 12-hour prolongation of a single light span, the following week by a 12-hour prolongation of a single dark span, etc.

Study A involved 93 controls and 96 shifted mice and was continued in the manner described until all mice died. The difference in mean survival time was six weeks, with the controls living longer. The difference was statistically significant (t=2.1; p < .05), Figure 1.<sup>20, 27, 40</sup>

At the time of this writing, Study B (involving 94 controls and 92 shifted mice) had reached the stage of about 53% overall mortality; at this stage 59% of the shifted animals and 48% of the control mice were dead. A test of this difference in mortality yielded  $\chi^2=1.77$ ; p < .10. Although these results were in the same direction as found in Study A,

the customary criterion for statistical significance ( $p < .05$ ) has not been achieved by Study B separately.

Data from the two similar studies were then pooled at a point when experimental mice in each study had been exposed to weekly LD-shifting for one year. After this span, 63% of the shifted mice and 49% of the control animals were dead ( $\chi^2 = 6.86$ ;  $p < .01$ ). Because there was a statistically significant difference between Studies A and B in the proportion of control mice dead one year after starting each study (due possibly to subtle environmental differences between the rhythmometry rooms and the environmental chambers), data were also pooled at comparable stages of mortality. At approximately 53% overall mortality in each study pooled data showed 59% of the shifted mice and only 45% of the control mice dead ( $\chi^2 = 6.77$ ;  $p < .01$ ).

Either method of pooling data from the available two studies indicates a statistically significant effect upon mortality of repeatedly inverting an environmental synchronizer of circadian rhythms, when such simulated shifts of environmental routine are initiated in adult life.<sup>26-40</sup> It is noteworthy, first, that this effect is recorded in a mammal and, second, that it is adverse for the species being investigated. Precisely because of this feature, such added work, including studies of non-human primates, urgently remains to be done. At the moment, direct extrapolation to human beings is not advocated.

However, with such evidence in hand, we turn again to the reduction in mean lifespan by about 6% found in Study A and shown in Figure 1 for mice subjected to once-weekly inversions (180°-shifts) of the lighting regimen starting in maturity.<sup>26,27,40</sup> These same data are visualized once more, as the second column in Figure 2, for a comparison with data on mice subjected to once-weekly schedule changes starting at conception. The lifespan of the latter group was not shortened. On the average, the mice on shifted schedules lived longer. This lengthening of lifespan, however, is not statistically significant.

One can not escape the view that changes in schedules affect a mammal rather differently as a function of when they are begun. What has been documented in this connection is a difference between effects of shifts started in maturity and early in life, i.e., in different chronobiological stages rather than as a function of an aging process. However, rhythms are known to change as a function of age<sup>12,22,65</sup> and genetics.<sup>66</sup> An exploration of the "best schedule" according to a proper test, taking all of these factors into account, is overdue.

It is from such a broad prospective that we emphasize that as a function of a certain age at which they were instituted and also dependent upon other factors relating to the chronogenetics<sup>13</sup> as well as the chronophysiology of rhythmic systems, repeated schedule shifts may be harmless, may be life-shortening or, perhaps, even life-lengthening.

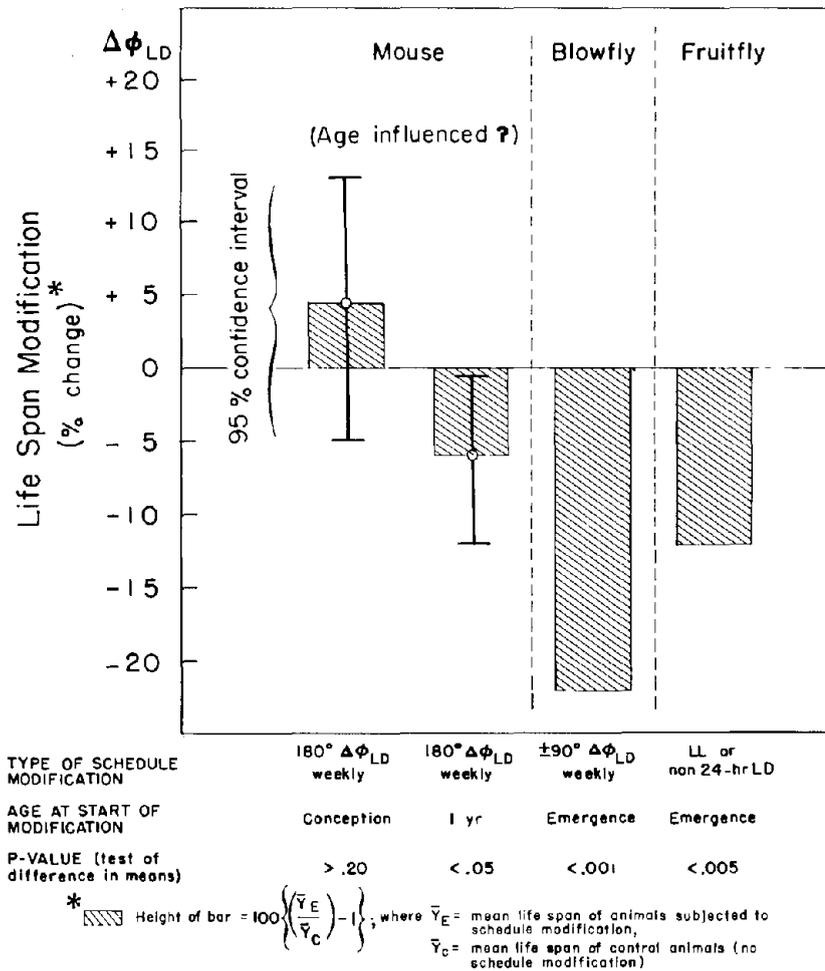
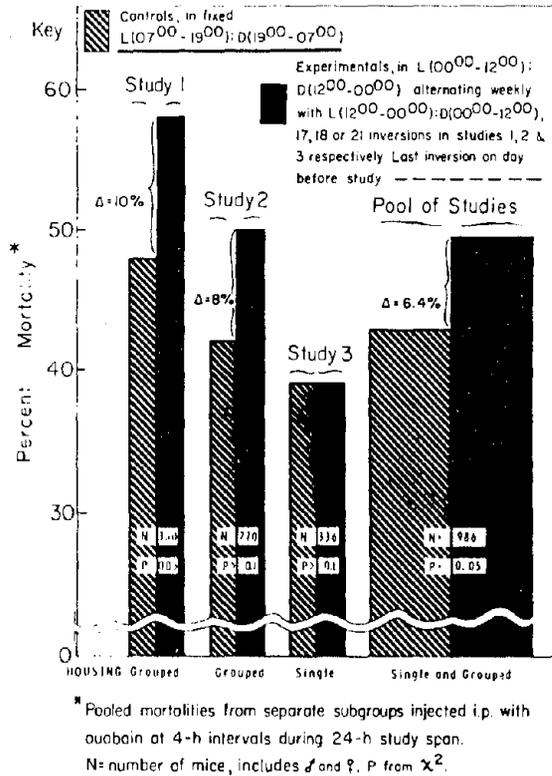


Figure 2. Effect of weekly shifting ( $\Delta\phi$ ) or other modifications of lighting schedule on life span of mice and insects.

Our findings in the sixties on life-shortening by schedule-shifts in mammals (cited in 40) should be complemented by the results of subsequent work involving lighting schedule manipulation on the blowfly by Aschoff<sup>5</sup>, the fruitfly by Pittendrigh<sup>60</sup>, Figure 2, and most recent work by Hayes on several insect species.<sup>34</sup>

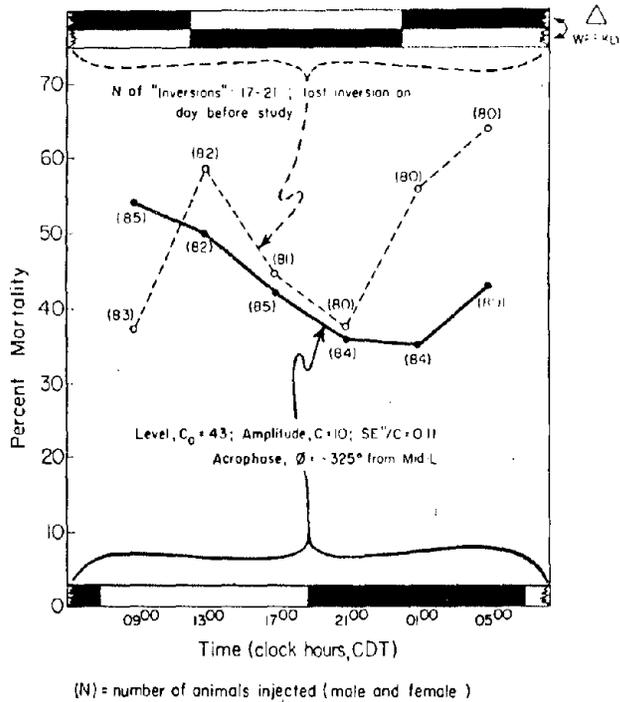
Figure 3 summarizes other experiments carried out in the sixties with Paul Mason at the Chronobiology Laboratories of the University of Minnesota involving the exposure to repeated changes in routine of either singly-housed or grouped animals. No difference in susceptibility to Qua-

Figure 3. Susceptibility of mice to Ouabain increased by 17 to 21 weekly inversions of lighting schedule; effect may depend on housing density.



Apparent Enhancement of Susceptibility to Ouabain in "Grouped" Inbred C-Mice Subjected to Repeated Synchronizer Inversions (Weekly Alternations in Timing of 24-h Light-Dark Cycles).

Susceptibility to Ouabain exhibits two peaks per 24 hours in mice subjected to schedule inversion as compared to a single peak in control animals.



bain, a cardiac drug simply used as a load, was found in the study on singly-housed animals subjected or not to 21 inversions of the lighting regimen. By contrast, in studies on commonly housed animals the weekly inversion of the lighting regimen resulted in a higher mortality. The latter suggests that resistance to loads will be lessened under conditions involving the interaction of repeated weekly schedule shifts with other burdens such as common housing.

## 2. Schedule-shifting and circadian rhythms.

An organism's circadian (about 24-hour) rhythms adjust gradually to a sudden change in synchronizing environmental schedules, such as the light-dark regimen for laboratory animals, Figures 4 and 5, or societal requirements for man, Figures 6a and 6b. For most mammalian functions at least several days elapse before the timing of circadian maxima (say, in a given performance function) is appropriately timed in relation to a new environmental routine.<sup>4, 8, 16, 33, 36, 41, 48, 61</sup> During this span of adjustment, the shifting organism may exhibit daily spans of (improperly-timed) relative advantage alternating with spans of relative disadvantage, in comparison with unshifted individuals, Figures 7-9.<sup>38, 43</sup>

The rates of adjustment of different circadian rhythms to changes in synchronizer schedules may differ within the same subject, Figure 10. The resulting alteration of time relations among rhythms lasts until all achieve resynchronization with the new schedule, Figure 11. Possibly because of such altered time relations the organism's overall performance may be altered (depressed or improved) for a considerable span after the change in schedule, Figure 12.

The rate and the extent of adjustment to a shift in external (possibly synchronizing) schedules depends not only upon the kind of function investigated for a rhythm with a given frequency but also upon the given species.

Table I reveals the dramatic difference in the rate of adjustment of a rhythm in nyctinasty of the silk tree on the one hand and that in oral temperature of human beings on the other hand and shows further that there is a directedness in most species in such a fashion that advances and delays occur at different rates.

Moreover, apart from rates of adjustment there may be differences in adjustability per se among different functions of one and the same organism. This can be documented for circadian rhythms in different variables of the same human volunteers: one variable may adjust largely, if not entirely, to a given new schedule (such as the rhythm in pH of human urine on a 21-hour routine of living), whereas the rhythm of other variables adjusted only partly if at all, Figure 13.

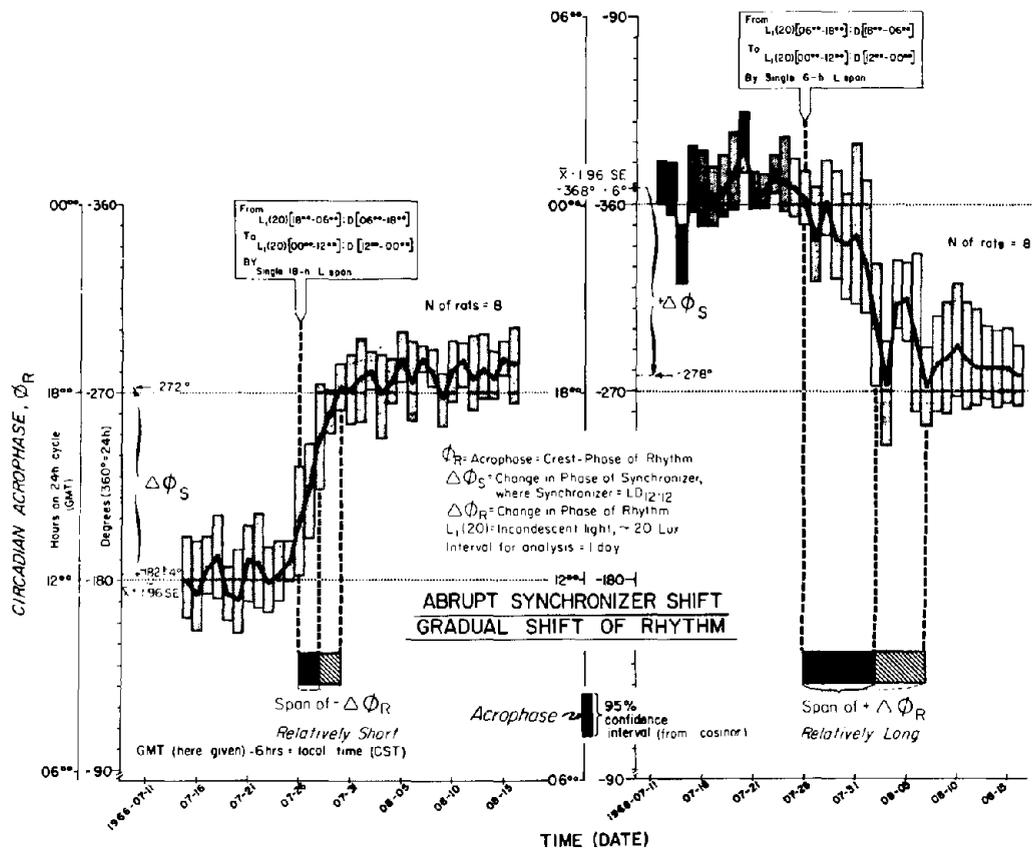


Figure 4. Phase shifting of 24-hr.-synchronized circadian rhythm in intraperitoneal temperature of female MSD rats: By 90° delay of lighting regimen (left). By 90° advance of lighting regimen (right). Rhythm acrophase ( $\phi_R$ ) on successive days following inversion of lighting schedule ( $180^\circ \Delta\phi_S$ ).  $\phi_R$  = timing of high point of 24-hour cosine curve fitted by least squares to four-hourly data on the three variables.

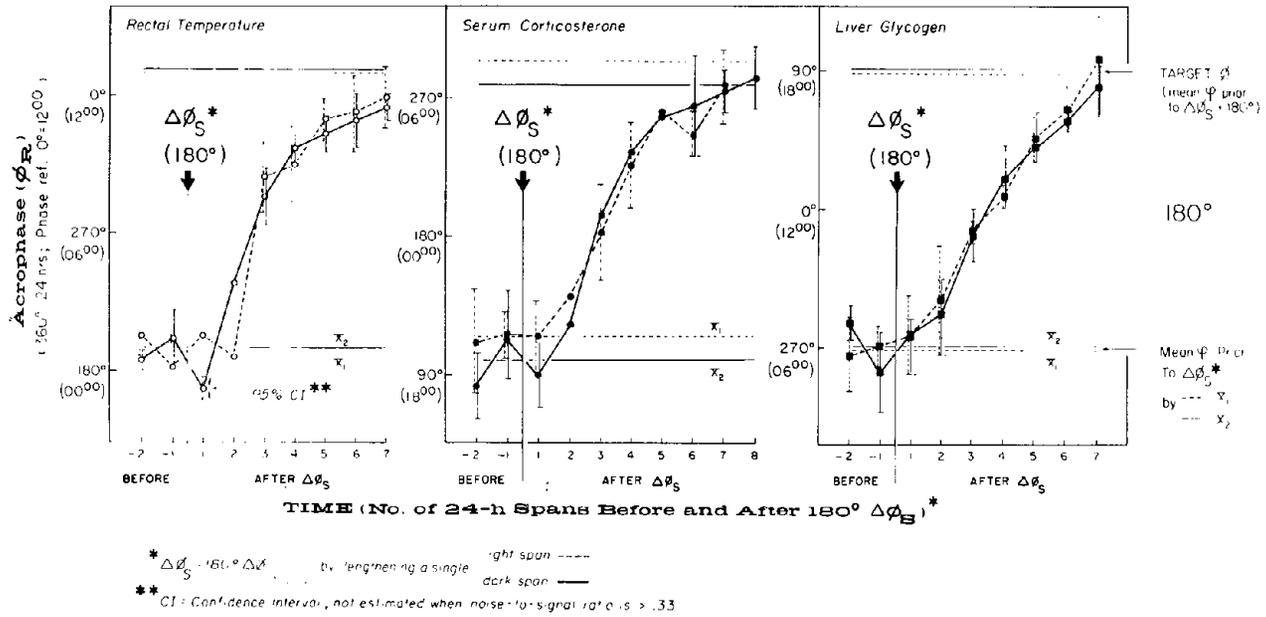


Figure 5. See Figure 4 legend. Separate study with results from control (unshifted) mice included.

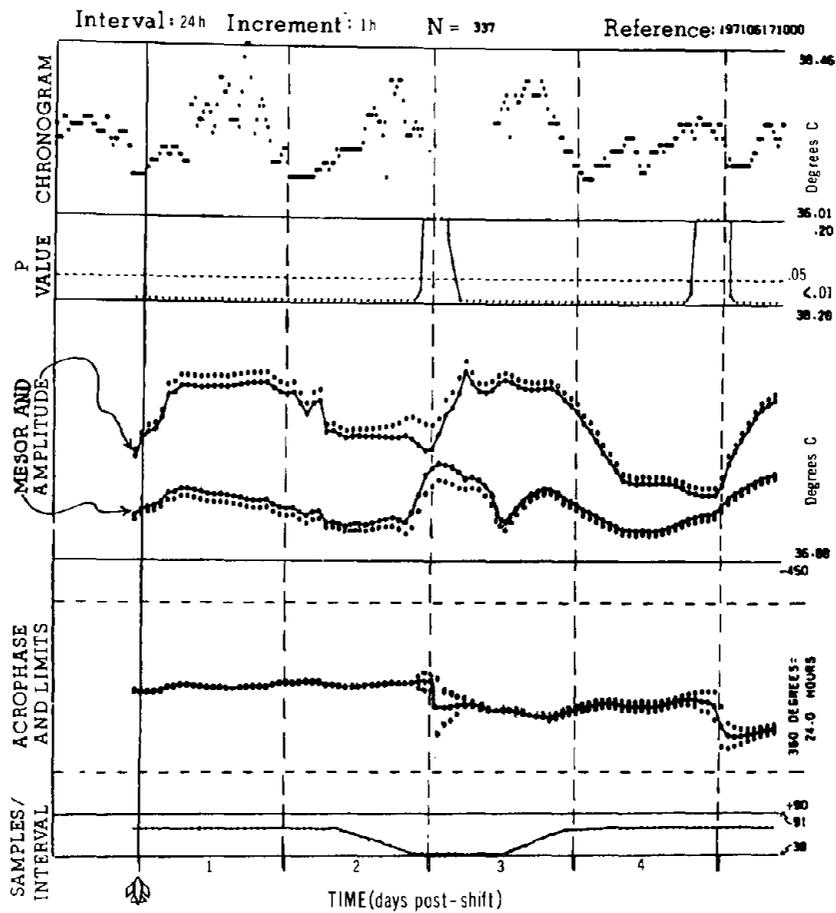


Figure 6a. Rectal thermograph (at 20'-intervals) in relation to transmeridian flight across six time zones (Mpls., Minn., USA to Bruxelles, Belgium. Data on rectal temperature (upper row) and parameters of circadian rhythm (rows 3 and 4) based on least squares fitting of 24-hour cosine curve to overlapping 24-hour section of data. Mesor = mean value of fitted curve; Amplitude =  $\frac{1}{2}$  peak-trough difference; Acrophase = timing of high point in relation to 00<sup>00</sup> Central Standard Time (marked twice by horizontal dashed lines in row 4 of figure). Acrophase advances only gradually following the flight.

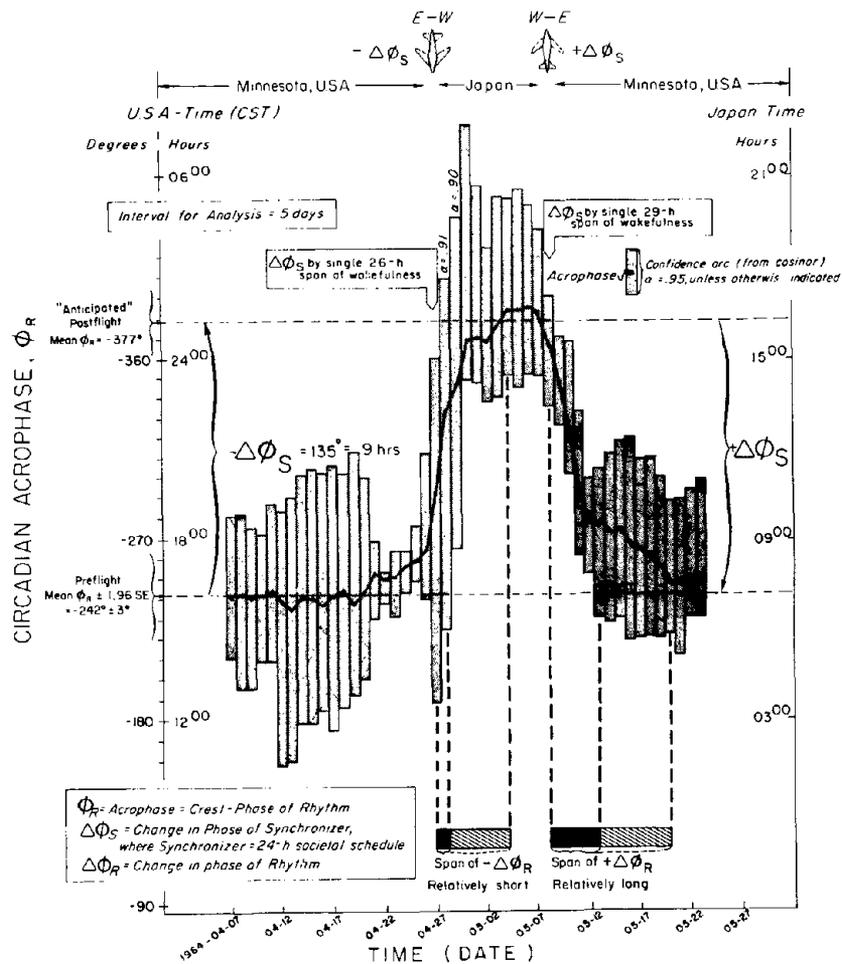


Figure 6b. Phase shifting of circadian rhythm in oral temperatures of 5 healthy adult white males.

Rhythm adjustment also may depend on such factors as: (1) its "free-running" circadian period (i.e., the endogenous period of the persisting circadian rhythm in the absence of known environmental synchronizers); (2) the kind, strength and number of the synchronizers acting upon the given variable, Figure 14; and (3) the direction of the shift (i.e., whether the schedule is moved forward or backward in time), Figures 15 and 16. These factors also may influence the organism's response, as shown by a performance decrement after a flight from west to east but not after a

TABLE 1

*Comparative Physiologic Studies on the Phase-Shifting of 24-Hour-Synchronized Circadian Rhythms Reveal Structured Adjustment in the Form of Differences in Rates of Rhythm Advance and Delay.*

| Organism                                   | Variable                      | Extent of Shift<br>in Synchronizing<br>Lighting Regime |         | Hours to Adjust to Regimen |       |            | Reference                          |
|--|-------------------------------|--|---------|----------------------------|-------|------------|------------------------------------|
|  |                               | Hours<br>(on a<br>24-hour<br>cycle)                    | Degrees | Advance                    | Delay | Difference |                                    |
|  |                               |  |         | Faster advance             |       |            |                                    |
| <i>Albizzia julibrissin</i> (silk tree)    | Pinnulè angle                 | 4 <sup>a</sup>   | 60      | ~24                        | ~52   | 28         | Koukkari and Halberg <sup>24</sup> |
| <i>Fringilla coelebs</i> , (chaffinch)     | Jumping activity              | 6  | 90      | ~60                        | ~120  | 60         | Aschoff and Wever <sup>6</sup>     |
|  |                               |  |         | Faster delay               |       |            |                                    |
| <i>Tribolium confusum</i> , (flour beetle) | O <sub>2</sub> consumption    | 6  | 90      | >48                        | >24   | 24         | Chiba et al <sup>8</sup>           |
| Sprague-Dawley rat                         | Intraperitoneal temperature   | 6  | 90      | ~312                       | ~120  | 192        | Halberg <sup>29</sup>              |
| Monkey (several species)                   | Auxiliary temperature         | 6  | 90      | >120                       | ~72   | 48         | Halberg <sup>17</sup>              |
| Man  | Oral temperature <sup>b</sup> | 6  | 90      | ~312                       | ~192  | 120        | Halberg <sup>16</sup>              |

<sup>a</sup>4 hours = ½ the dark span in *Albizzia*. 6 hours = ½ the dark span in rat, monkey, and chaffinch.

<sup>b</sup>In social setting. Studies by Aschoff<sup>3</sup> on men isolated in a bunker reveal faster advance than delay.

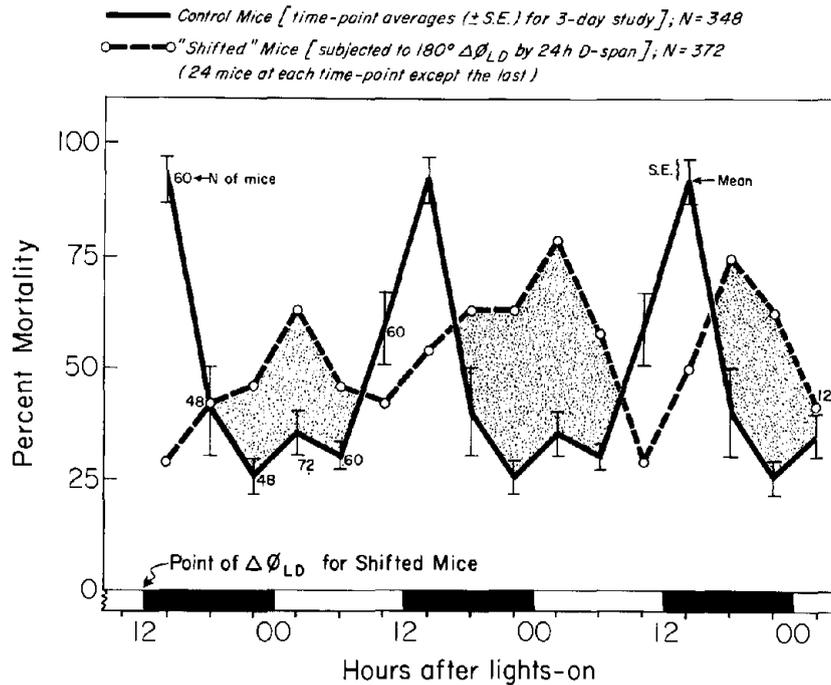


Figure 7. Mortality following single injection of ethanol (6 mg/kg, i.p.) into separate groups of shifted and unshifted mice at different stages of the lighting regimen. Shading indicates spans of relative disadvantage for shifted mice.

flight in the opposite direction, Figure 17. Rhythms also may differ in their adjustment to an unusual schedule, Figure 13.

The rate and the extent of adjustment to a shift in external schedules depends also upon the given subject. This fact was suspected from comparative studies on the effects of schedule shifts, with or without geographic displacement such as that necessitated by transmeridian flights.<sup>15, 24, 30, 51</sup> It is supported by results noted on experimental animals<sup>17, 18, 65</sup> and human beings.<sup>54, 55, 56</sup> For the mouse, studies of single and repeated lighting regimen inversions both suggest (although they do not prove) a marked role of age in determining the rate of shift for the circadian body temperature rhythm.

Single phase-shifts of the lighting regimen carried out on several inbred strains of mice further suggest interactions between age and genetics with respect to the shift rate of the body temperature rhythm. Rectal

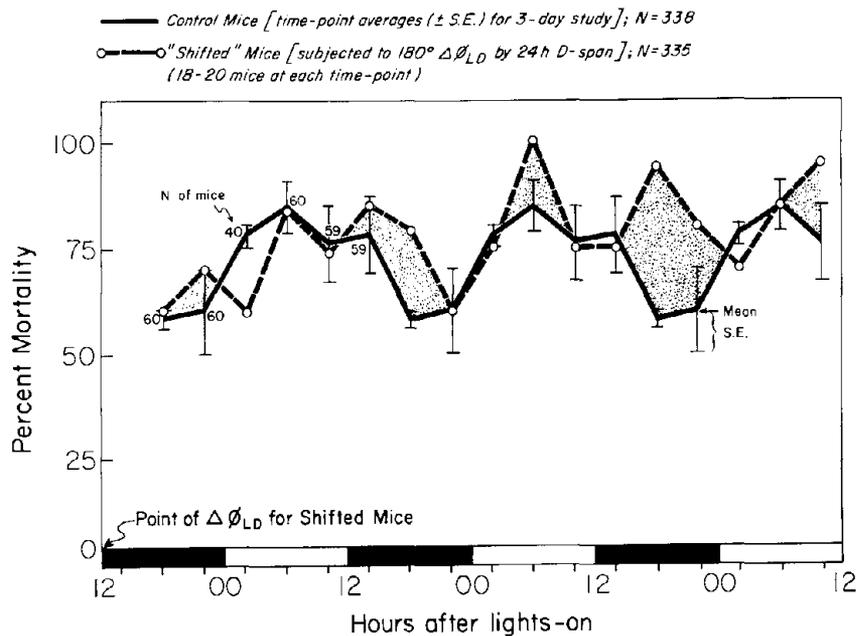


Figure 8. See legend to Figure 7. In this case Ouabain was injected (8 mg/kg. i.p.).

temperature was measured by thermistor bridge circuit at 4-hour intervals for 10 days on animals of several genetically defined stocks. A 90°-shift of the lighting regimen (LD<sub>12:12</sub>) was carried out on day 3 and a 180°-shift of lighting regimen on day 6. Data were analyzed by the fit of a 24-hour cosine curve to all values available for each of 10 consecutive 24-hour spans. The original acrophases prior to the first lighting regimen shift agreed within 1.5 hours (22°). By contrast, near the end of the second lighting regimen shift, the oldest animals were lagging in acrophase behind the younger ones. For mice of corresponding age there were also marked differences in shift rate as a function of genetic background. Thus a cumulative effect of two consecutive phase-shifts of an LD<sub>12:12</sub> lighting regimen [a first six-hour (-90° Δφ<sub>8</sub>) and a subsequent 12-hour prolongation of a single light span (-180° Δφ<sub>8</sub>)] served for isolating strain or age difference in shift behavior of circadian rhythms in rectal temperature

of inbred CBA or NZB mice [assessed by circadian acrophase,  $\phi$ ], Table 2.

The difference in adjustment described above was observed on animals that were subjected to the burden of being picked up for each temperature measurement. Therefore, these results need not apply in the absence of imposed burdens. For instance, singly-housed animals monitored by temperature telemetry may not exhibit similar differences.

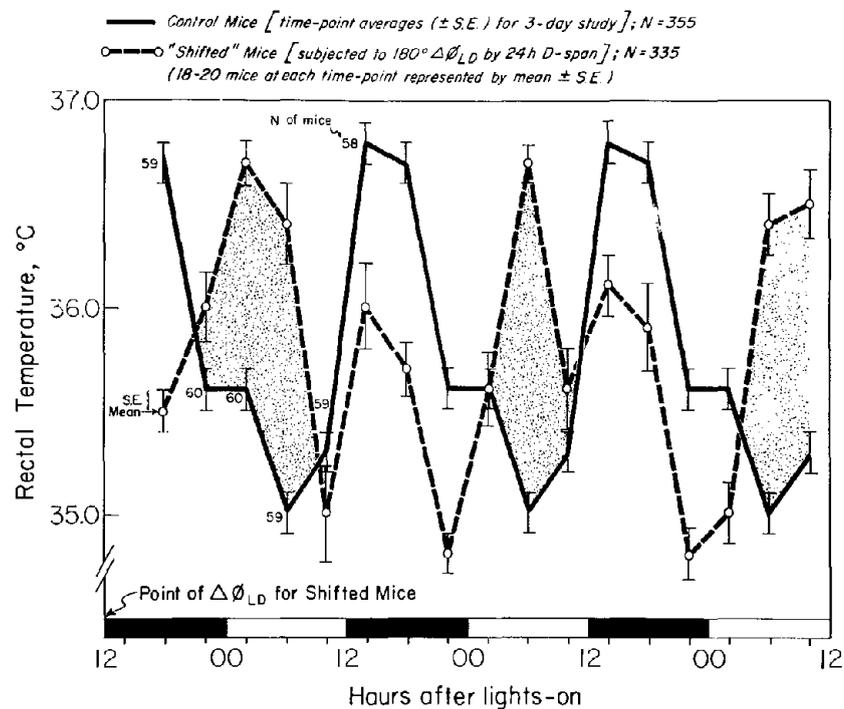
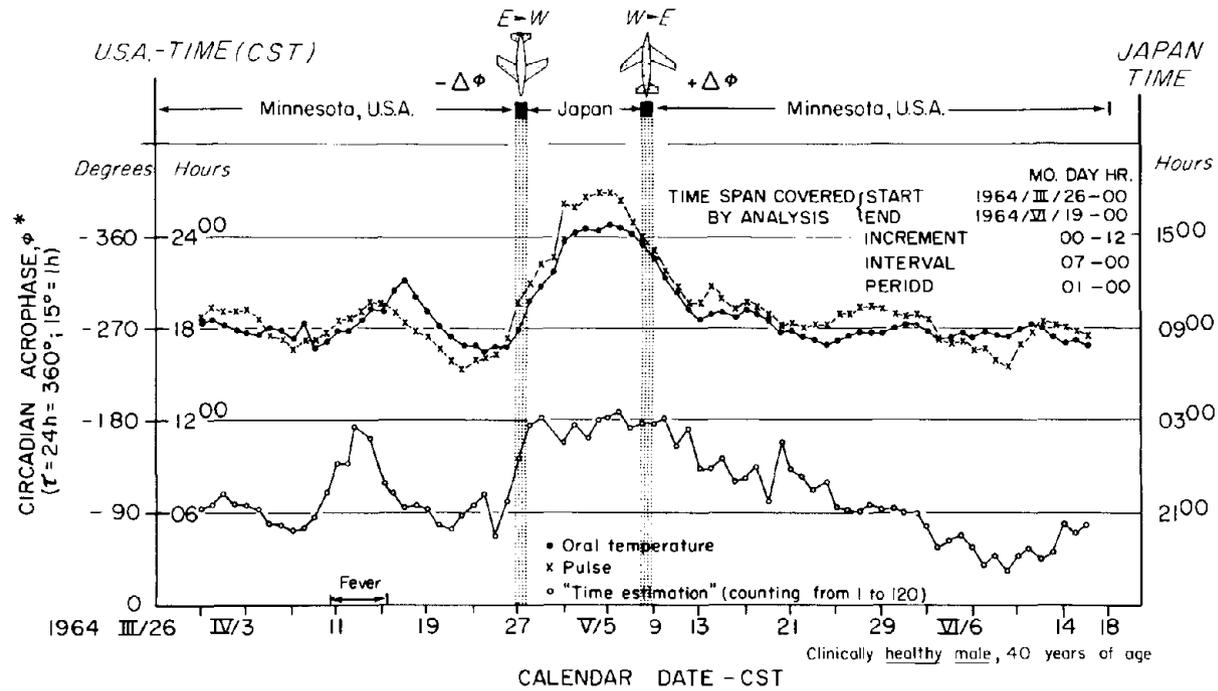


Figure 9. Rectal temperature in separate groups of mice sampled at different stages of lighting regimen in shifted and unshifted mice. Shading indicates spans of relative disadvantage for shifted mice, assuming temperature is a gauge of performance capability.





\* Phase Reference: start-time of analysis.

Data collection started 06<sup>55</sup>, III/26/1964 and ended 22<sup>26</sup>, VI/19/1964.

Figure 11. Changes in acrophase relation among circadian rhythms due to differences in rate of adjustment to westward and eastward flights.

TABLE 2

| Animals investigated |       | Computative acrophases $\pm 1.96$ SE* |              |               |
|----------------------|-------|---------------------------------------|--------------|---------------|
| Mouse strain         | Age** | $\phi_1$                              | $\phi_2$     | $\phi_3$      |
| NZB : CBA            | y     | -349 $\pm$ 11                         | -74 $\pm$ 14 | -217 $\pm$ 23 |
|                      | o     | -333 $\pm$ 19                         | -81 $\pm$ 28 | -161 $\pm$ 25 |
| NZB                  | y     | -342 $\pm$ 12                         | -70 $\pm$ 24 | -192 $\pm$ 13 |
|                      | o     | -339 $\pm$ 16                         | -83 $\pm$ 20 | -166 $\pm$ 21 |
| CBA                  | y     | -331 $\pm$ 12                         | -71 $\pm$ 16 | -136 $\pm$ 10 |
|                      | o     | -307 $\pm$ 19                         | -71 $\pm$ 31 | -114 $\pm$ 24 |
| A/JAX                | y     | -346 $\pm$ 16                         | -58 $\pm$ 14 | -149 $\pm$ 13 |
|                      | o     | -315 $\pm$ 22                         | -61 $\pm$ 25 | -166 $\pm$ 20 |

\*  $\phi_1$  = Pre-shift acrophase ref. to 00<sup>00</sup> local time (LO6<sup>00</sup> - 18<sup>00</sup>).  
 $\phi_2$  = Day 4 post -90°  $\Delta\phi_s$  (LO6<sup>00</sup> - 18<sup>00</sup> to L12<sup>00</sup> - 00<sup>00</sup> by prolongation of light)  $\phi$  ref. is  $\phi_1$ ; target  $\phi$  is -90° from  $\phi_1$ .  
 $\phi_3$  = Days 3 and 4 post -180°  $\Delta\phi_s$  (L12<sup>00</sup> - 00<sup>00</sup> to L00<sup>00</sup> - 12<sup>00</sup> by prolongation of light)  $\phi$  ref. is  $\phi_1$ ; target  $\phi$  is -270° from  $\phi_1$ .  
 \*\* y = 'Younger' animals (2-6 m of age); o = 'older' animals (10-20 m of age).

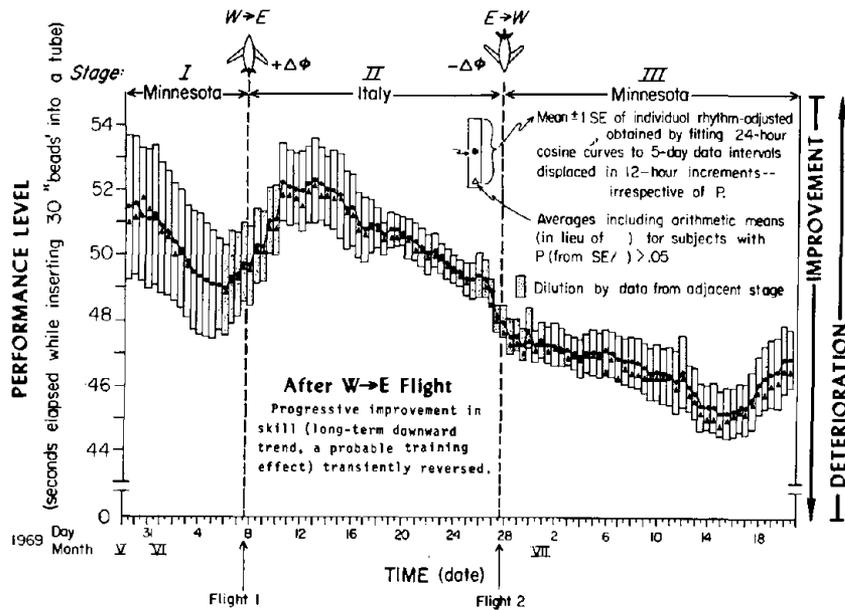


Figure 12. Data on "eye-hand skill" of 7 healthy subjects (measured as time required to insert fixed number of beads into closely-fitting tube), obtained before, during and after a visit to Europe, are shown in top row. Overlapping 20 day sections of these data were fitted with 24-hour cosine curve by least squares to derive "moving estimates" of circadian amplitude, mesor (row 3) and acrophase (row 4). Changes in mesor (average value of fitted curve) indicate a performance decrement (i.e., a longer time was required to complete the task) while in Europe and for some time after return to U.S.

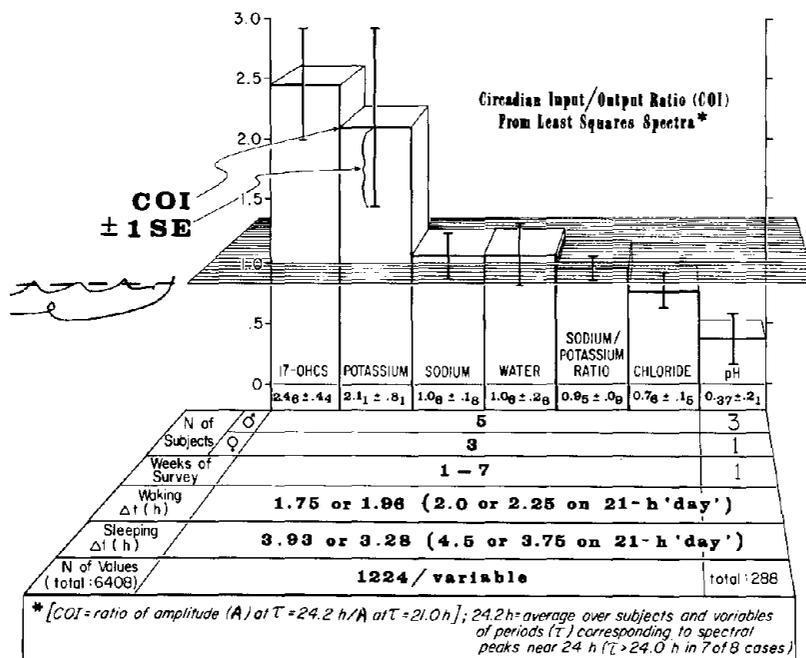


Figure 13. Circadian gradation by endogenicity (above shaded area) vs. exogenicity (below shaded area) of urinary variables in presumably healthy human beings on a 21-hour day routine ( $\tau$ s) in arctic summer — Spitsbergen ( $78^\circ N$ ). Men continue to exhibit predominantly circadian (24.2 hour) rhythm in excretion of some variables (corticosteroids and potassium) while some other rhythms are influenced to a greater but varying extent by the imposed periodicity — the circadian rhythm in urinary pH being most dependent upon the environment schedule.

To turn to human beings, studies of rhythm-shifting on individuals resting in isolation who change schedules without the loads associated with work are not comparable to field studies on actual shift workers. From a field study carried out by the use of autorhythmometric procedures<sup>25, 53</sup> Reinberg et al<sup>13, 54</sup> have reported a relatively quick adjustment (within one to seven days) of the circadian acrophase of a set of 17 variables, including oral temperature, grip strength, urinary K, Na, 17-OHCS, and 5-hydroxytryptamine. These authors studied 20 shift workers of an oil refinery during seven consecutive weeks. An eight-hour shift of work-times was instituted each week. A quick adjustment of the investigated circadian acrophases occurred without a detected statistically significant difference between the adjustment following advances and delays of the socio-ecologic synchronizer.

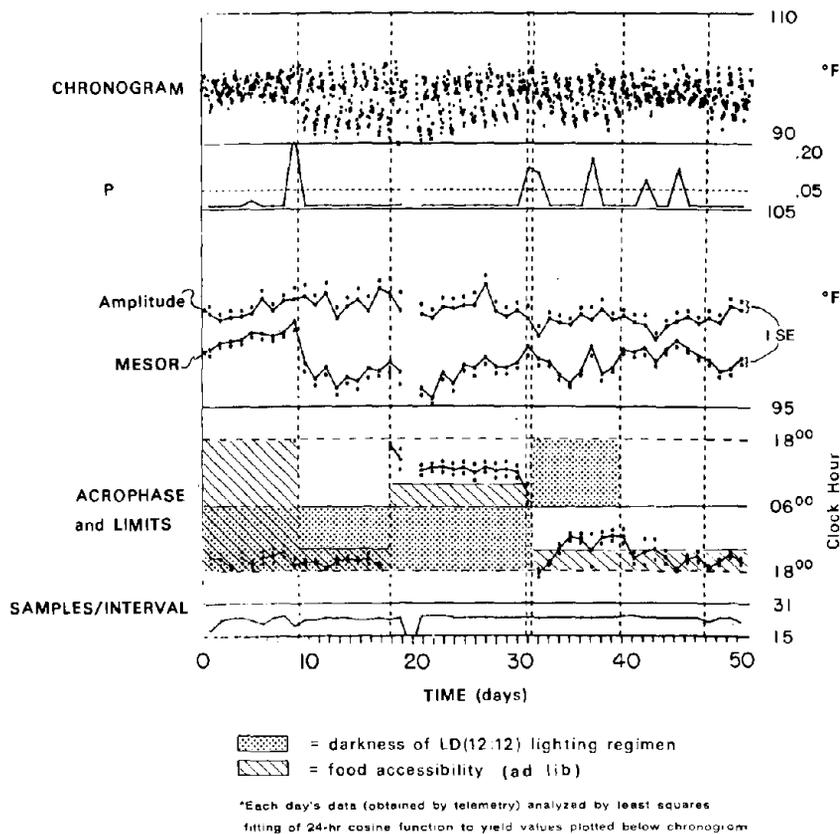


Figure 14. Circadian temperature rhythm of mouse affected by time-restricted food accessibility, interacting with lighting regimen. During a 50-day observation span, telemetered intraperitoneal temperatures, graphed in the top row, reveal the interaction of two prominent synchronizers of the murine circadian system — regimen of light and darkness alternating at 12-hour intervals and the time of restricted access to food. During a first 10-day span while food is available ad libitum, the body temperature rhythm is synchronized by light and darkness. During an ensuing span, there is a large increase in amplitude (with a drop in mesor) while food is restricted to the first four hours of darkness each day. In this case of positive synchronizer interaction, the acrophase lies within the early dark span and the time of access to food. During a third span of negative synchronizer interaction, the access time to food “competes” with darkness; during this stage, the acrophase lies in an intermediate position, as it does also in the fourth span when each of the synchronizers is reversed. During a fifth stage, while the animals are kept in continuous light, with access time to food the only synchronizer, the acrophase again rapidly moves into the time of food availability.

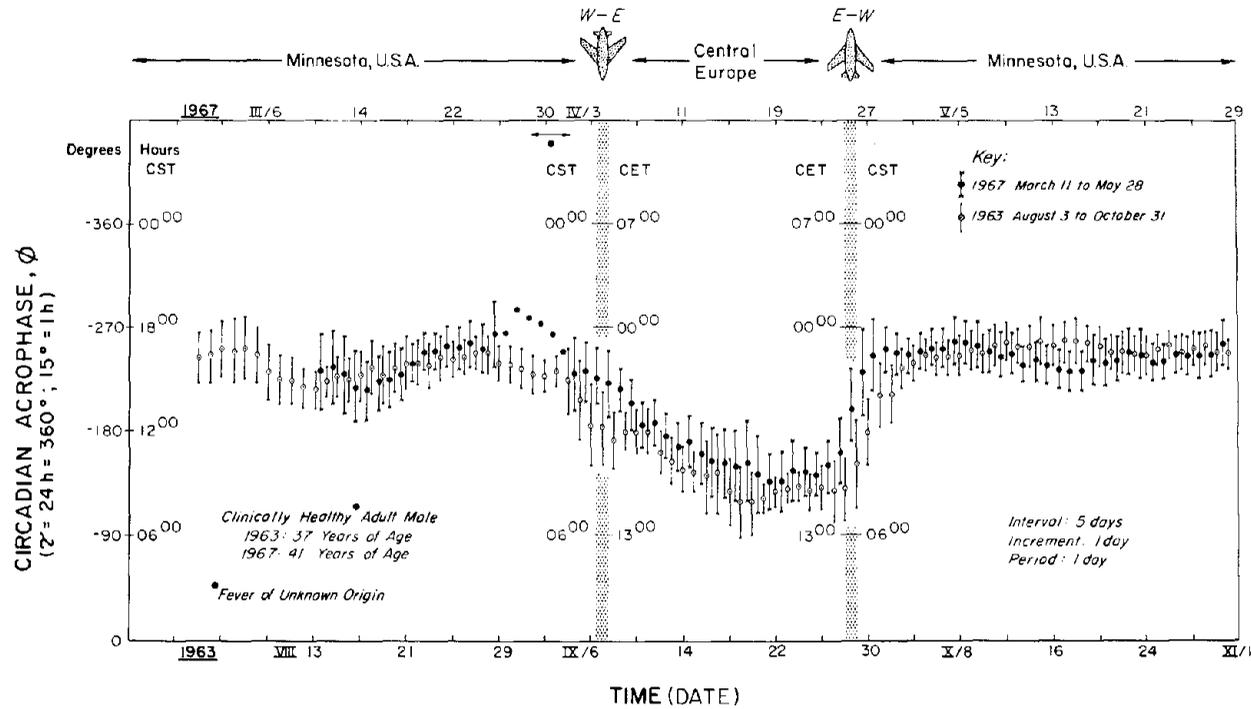


Figure 15. Phase shifts of circadian rhythm in oral temperature as a result of two intercontinental flights by the same subjects in 1963 and 1967. Rate of resynchronization of circadian temperature rhythm in a man is more rapid following a seven-hour delaying shift of daily schedule (westward flight) than after an advancing shift (eastward flight).

These studies have been followed up in a second survey performed again on shift workers in an oil refinery, subjected to a shift in schedule every three or four days (A. Reinberg and N. Vieux, unpublished data). The subjects involved in these field studies had worked on shifts for at least one year. Their adjustment again was rapid. However, they were selected subjects since within a few months a man not "able" or "gifted" for shift work usually drops out from this type of employment.<sup>62, 63</sup>

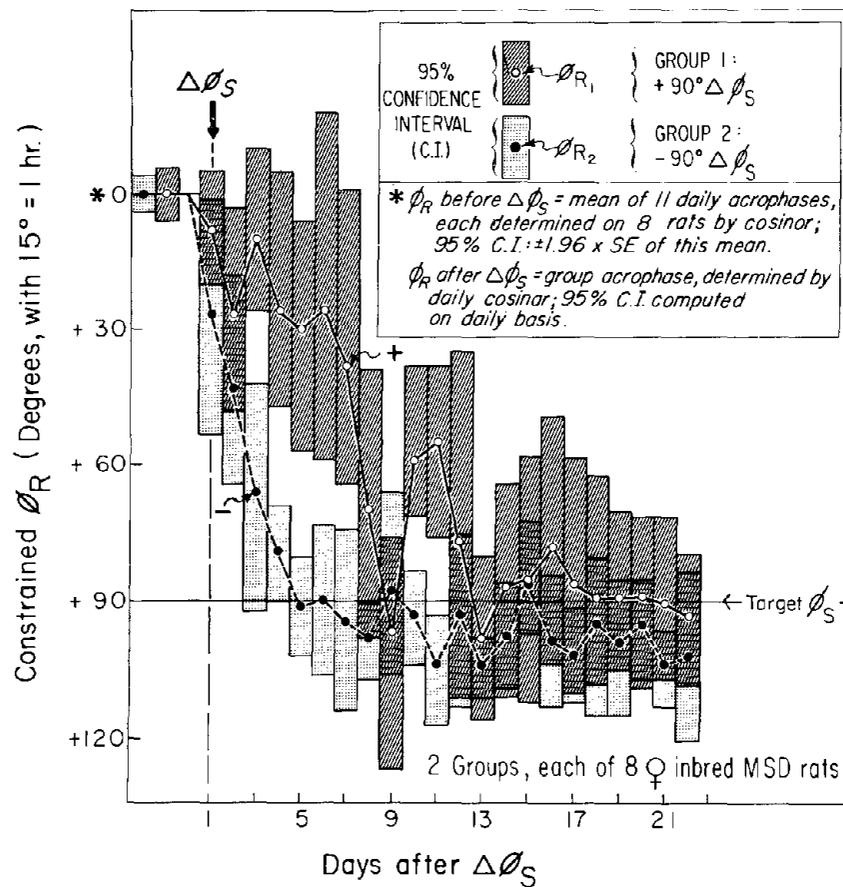


Figure 16. Difference in shift-behavior of circadian acrophase,  $\phi_R$ , for intraperitoneal temperature after a  $90^\circ$ -advance (+) or delay (-) of  $\Delta \phi_S$  ( $LD_{12:12}$ ). Rate of resynchronization of circadian temperature rhythm in rats is more rapid after a six-hour delaying shift of lighting regimen than after an advancing shift.

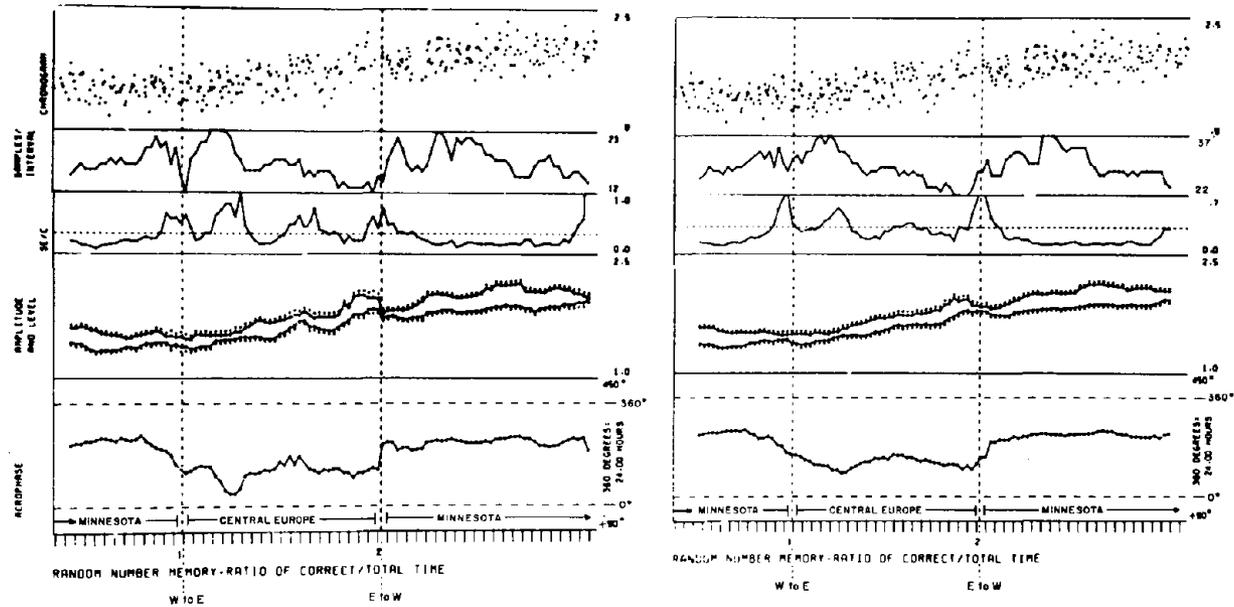


Figure 17. Phase shift of a circadian performance rhythm after flights from west to east and east to west resolved by chronobiological profiles on the same data each carried out with the fit of a 24-hour period to 72-hour (left) or 120-hour (right) intervals displayed by 12-hour increments. Acrophase reference = local midnight; one division on abscissa = 1 day; healthy young adult male—22 years of age. Rhythm-adjusted average time required to perform fixed task increases temporarily followed eastward flight (advancing shift) but not after westward flight.

### 3. Age, circadian rhythms and shift work.

Quite often, ill-defined psycho-social as well as physiologic considerations lead to the suggestion that older individuals should not be introduced to rotating duties or shift work because adjustability declines with age and eventually productivity is reduced and health may suffer.

There are suggestive similarities between the changes an organism undergoes cyclically during a 24-hour span and those it experiences unidirectionally with age. Mature mice exhibit about as great a change in sensitivity to a barbiturate during the course of a day as they do while aging over a considerable fraction of their adult life.<sup>42</sup> The elasticity of connective tissue in mice decreases with advancing age but also declines during one part of the day to "recover" at another.<sup>39</sup> A man's response to a fixed work load (measured in terms of an increase in heart rate or in the feeling of fatigue) resembles that of an older person if the work is performed at night.<sup>46</sup>

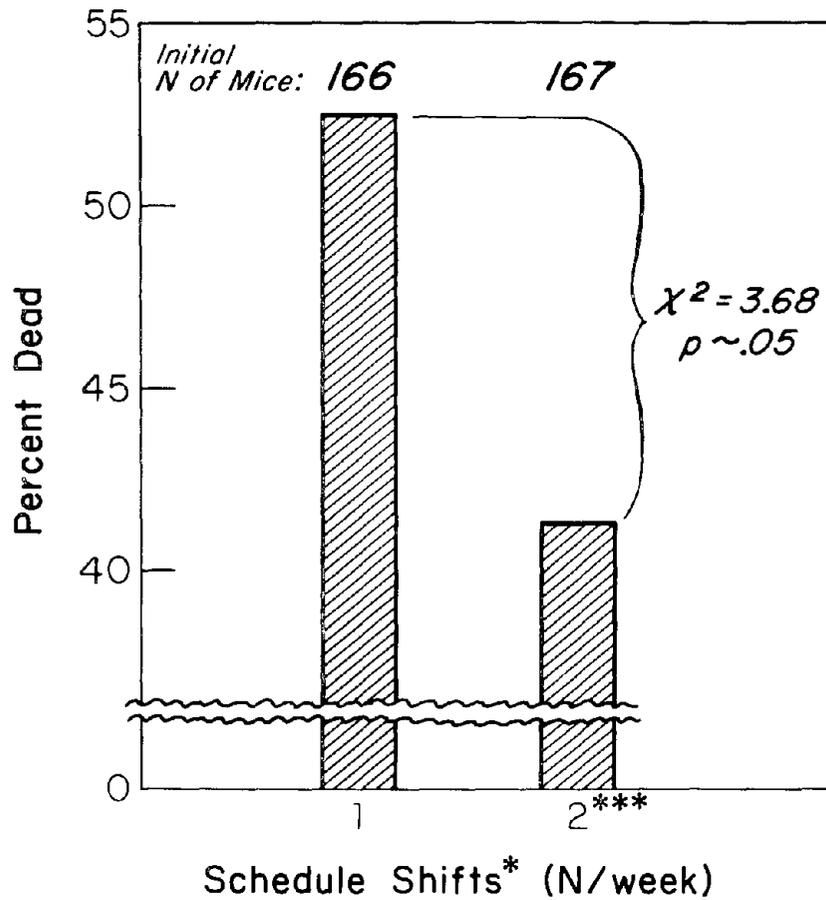
Characteristics of at least some circadian rhythms appear to change during the aging of adult animals. The amplitude of the temperature rhythm tends to be lower in older mice and rats<sup>22,45</sup> as is the amplitude of rhythms in catecholamine excretion of aging human beings.<sup>12</sup> Changes in the frequency<sup>49</sup> and overall average<sup>12,45</sup> of circadian rhythms also have been reported. An age-dependence of the rate at which circadian rhythms shift has been observed in laboratory animals.

Thus, for mice of several strains, advancing age leads to a slower adjustment of the circadian rhythm in rectal temperature following a change in lighting routine. This was gauged objectively by differences in the gradual displacement rate of the acrophase (i.e., the timing of the peak in a 24-hour cosine curve best approximating the given data) of the rectal temperature rhythm in animals sampled repeatedly at four-hour intervals.<sup>60</sup> Will such observations and others lead us to understand why a shortening of the lifespan of animals subjected to repeated shifts during maturity was not detected when such shifts were initiated early in life, as documented in Figure 2? We must inquire not only into any critical age but also into the comparative physiologic differences in extent of lifespan reduction, so different in rodent and inscct. Are differences in metabolic rate or the presence of a temperature regulating mechanism pertinent?

Differences in the speed of acrophase adjustment as a function of the subject age have been observed in shift workers by Reinberg et al<sup>54,56</sup> for only one of the many variables studied — oral temperature. The rate and hence the extent of  $\phi$  adjustment was faster for subjects 25 to 30 years of age than for older shift-workers.

Ongoing studies in our laboratory examine further the possibility that schedule shifts repeated twice a week are tolerated better than shifts carried out once weekly, Figure 18. Such studies eventually should provide a physiologic basis for deciding on the merits of a practice prompted

Frequency of Schedule Shifts\*  
 Instituted from Weaning May Affect  
 Mammalian Mortality\*\* Later in Life



- \*Inversions (of regimen of light for 12 hours alternating with darkness for 12 hours) by prolonging, in alternation, a 12-hour span of light or darkness into a 24-hour span =  $180^\circ \Delta\phi_{LD12:12}$ .
- \*\*Pooled results from 2 studies on female BALB/c mice, near 47% overall mortality.
- \*\*\*Every 3 or 4 days.

Figure 18. Murine studies on simulated shift work suggest that an increase in frequency of changes in schedule need not be a disadvantage.

usually by psychologic or social considerations, namely, the choice of rapidly rotating shifts (c.g., every third day) over the long-term adherence to odd work schedules. In any event, often-repeated shifts and shifts initiated early in life may be less costly in terms of health and longevity than are shifts done less frequently and/or started later in life.

It is interesting to note that from both the clinical and the social points of view, fast rotations, i.e., schedule shifts repeated every two, three or four days (instead of every week) are well accepted and apparently well tolerated, insofar as one may judge from medical records as well as ballots and Gallup polls among shift-workers.<sup>1, 2</sup>

4. Relations among murine or human circadian physiologic rhythms at different organization levels can be manipulated by meal-timing — to change outcome of therapy.

Circadian rhythms in physiological, biochemical and pharmacological variables were investigated in mice restricted to feeding in either early light or early darkness or in human volunteers eating a single daily meal, as breakfast only or as dinner only. The timing and pattern of these changes during a 24-hour span is considerably different between mice feeding in early light and those feeding in early darkness.<sup>45, 47, 60</sup> As a consequence of these differences, internal relations among rhythms are affected. This effect becomes readily apparent when 24-hour cosine curves are fitted to such data. The relation among circadian rhythms in rectal temperature, liver glycogen and corneal mitoses differs as a function of whether feeding is permitted in early light or early darkness, Table 3.

Recent results of Lakatua, Haus et al at Minnesota<sup>47</sup> also are pertinent. Volunteers provided samples of blood at four-hour intervals for 24-hour spans — after they had, for three weeks, eaten a limited free-choice diet only within the two hours following awakening each day (breakfast only) or, again for three weeks, had not eaten before 12 hours after awakening each day (dinner only). A different internal timing between the circadian rhythms of adrenal cortical hormone and iron in human blood was found as a function of whether the individuals ate breakfast only or dinner only.

Whether altered time relations among rhythms can alter the body's overall functioning or behavior constitutes a question that requires much further study in relation to environmental effects upon rhythms. Figure 19 shows that in the rat the effect of carcinostatic treatment is not only dependent upon circadian state but depends further upon whether the animals eat a single meal at an unusual time rather than eating ad libitum.

5. Timing of circadian tolerance rhythm to an antineoplastic and antibiotic drug can be changed.

The circadian rhythm in another important variable, susceptibility to toxic effects of a carcinostatic drug, adriamycin, is also markedly af-

TABLE 3  
Parameters of circadian rhythms on different feeding schedules<sup>1</sup>

| Group <sup>2</sup>                     | Number of measurements | Mesor<br>±SE | Amplitude<br>±SE | Acrophase              |                         | SE  | P <sup>3</sup> |
|--|------------------------|--------------|------------------|------------------------|-------------------------|-----|----------------|
|  |                        |              |                  | Hr after feeding onset | Hr after lighting onset |     |                |
| <i>Rectal temperature, °C</i>          |                        |              |                  |                        |                         |     |                |
| I, M and F                             | 129                    | 36.9 ±0.09   | 1.13±0.12        | 5.8                    | 5.8                     | 0.4 | <0.01          |
| II, M and F                            | 119                    | 36.9 ±0.08   | 1.57±0.11        | 4.5                    | 16.5                    | 0.3 | <0.01          |
| III, M and F                           | 134                    | 37.0 ±0.07   | 0.69±0.10        | 4.1                    | 16.1                    | 0.6 | <0.01          |
| <i>Liver glycogen, %</i>               |                        |              |                  |                        |                         |     |                |
| I, M                                   | 24                     | 5.95±0.47    | 3.98±0.66        | 11.4                   | 11.4                    | 0.6 | <0.01          |
| II, M                                  | 24                     | 6.19±0.42    | 3.68±0.59        | 11.8                   | 23.8                    | 0.6 | <0.01          |
| III, M                                 | 24                     | 3.97±0.22    | 2.50±0.31        | 10.1                   | 22.1                    | 0.5 | <0.01          |
| <i>Liver glycogen, total mg</i>        |                        |              |                  |                        |                         |     |                |
| I, M                                   | 24                     | 75.9 ±7.0    | 58.0 ±9.9        | 11.2                   | 11.2                    | 0.7 | <0.01          |
| II, M                                  | 24                     | 74.6 ±6.0    | 51.4 ±8.5        | 11.4                   | 23.4                    | 0.6 | <0.01          |
| III, M                                 | 24                     | 52.6 ±2.9    | 36.6 ±4.1        | 10.1                   | 22.1                    | 0.4 | <0.01          |
| <i>Serum corticosterone, µg/100 ml</i> |                        |              |                  |                        |                         |     |                |
| I, M                                   | 12                     | 19.5 ±2.7    | 14.4 ±3.9        | 20.4                   | 20.4                    | 1.0 | 0.02           |
| I, M and F                             | 24                     | 21.0 ±1.7    | 11.7 ±2.3        | 19.7                   | 19.7                    | 0.8 | <0.01          |
| II, M                                  | 12                     | 22.8 ±5.1    | 9.0 ±7.2         | 20.2                   | 8.2                     | 3.0 | 0.48           |
| II, M and F                            | 24                     | 22.4 ±3.3    | 12.3 ±4.7        | 20.4                   | 8.4                     | 1.5 | 0.05           |
| III, M                                 | 12                     | 15.5 ±0.7    | 2.2 ±1.0         | 21.2                   | 9.2                     | 1.8 | 0.16           |
| <i>Corneal mitoses, N/1,000 cells</i>  |                        |              |                  |                        |                         |     |                |
| I, M                                   | 35                     | 8.38±0.44    | 3.34±0.61        | 21.1                   | 21.1                    | 0.7 | <0.01          |
| II, M                                  | 28                     | 8.36±0.63    | 4.72±0.92        | 16.5                   | 4.5                     | 0.7 | <0.01          |
| III, M                                 | 43                     | 7.31±0.41    | 5.73±0.59        | 15.1                   | 3.1                     | 0.4 | <0.01          |

<sup>1</sup>Parameter estimates based on least squares fitting of 24-hour cosine function: mesor, average value of rhythm; amplitude, ½ peak-trough difference; acrophase, time of highest value in hours after feeding onset and also in hours after lighting onset. <sup>2</sup>Group I was allowed access to food only during the first 4 hours of the daily L span, group II only during the first 4 hours of D and group III ad libitum; M, males; F, females. <sup>3</sup>P from F test: probability of obtaining F equal to or exceeding observed F if there were no 24-hour sinusoidal variation.

ected by meal-feeding. Mice feeding ad libitum are least sensitive to the drug if it is administered in the latter part of the daily light span. On the other hand, if feeding is permitted only during the early light span the susceptibility rhythm is shifted about 180°, regardless of whether the drug dose is given in proportion to body weight or is fixed, Figure 20.

#### 6. Lower body weights in man and mouse fed "breakfast" only.

Mice restricted to feeding in early darkness weighed less than those feeding in early light. That is, allowing these nocturnal animals to eat only at the beginning of their usual span of activity resulted in a lower body weight than was the case when feeding was permitted in early light, at which time, under *ad libitum* conditions, mice tend to be inactive.<sup>45</sup>

A similar observation has been made in the Chronobiology Laboratories of the University of Minnesota for the case of human beings. If the daily food allotment (2000 calories) was consumed as breakfast, subjects

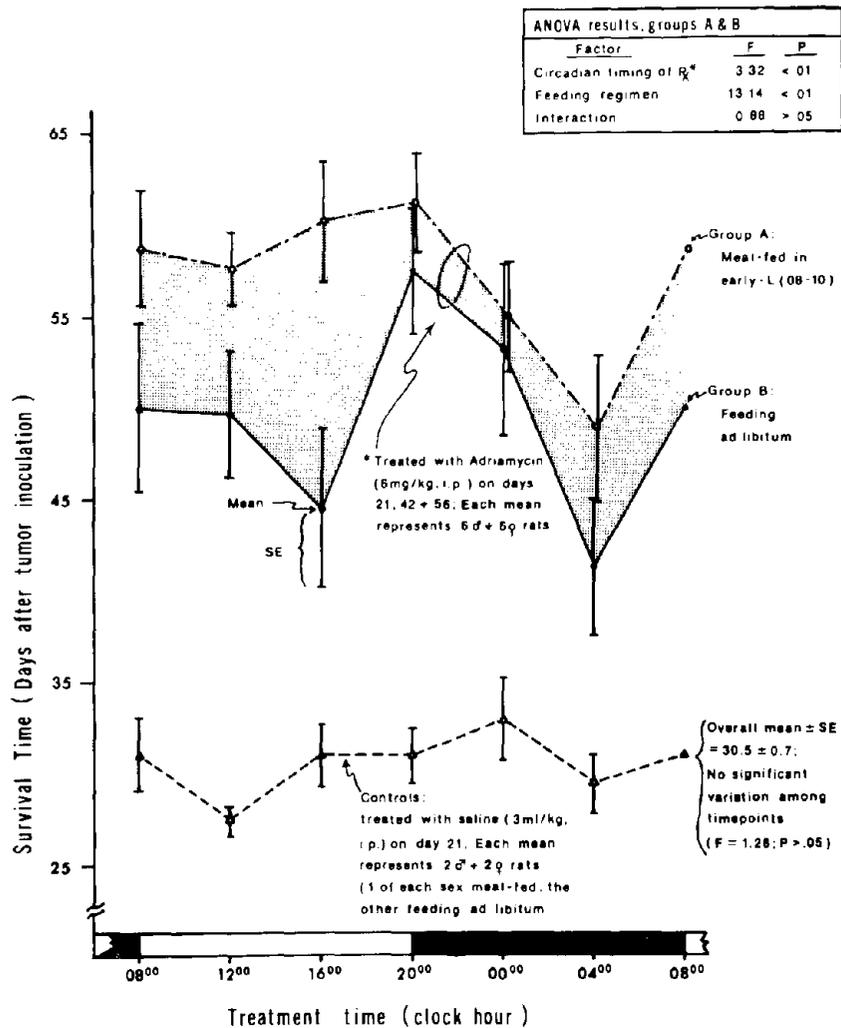
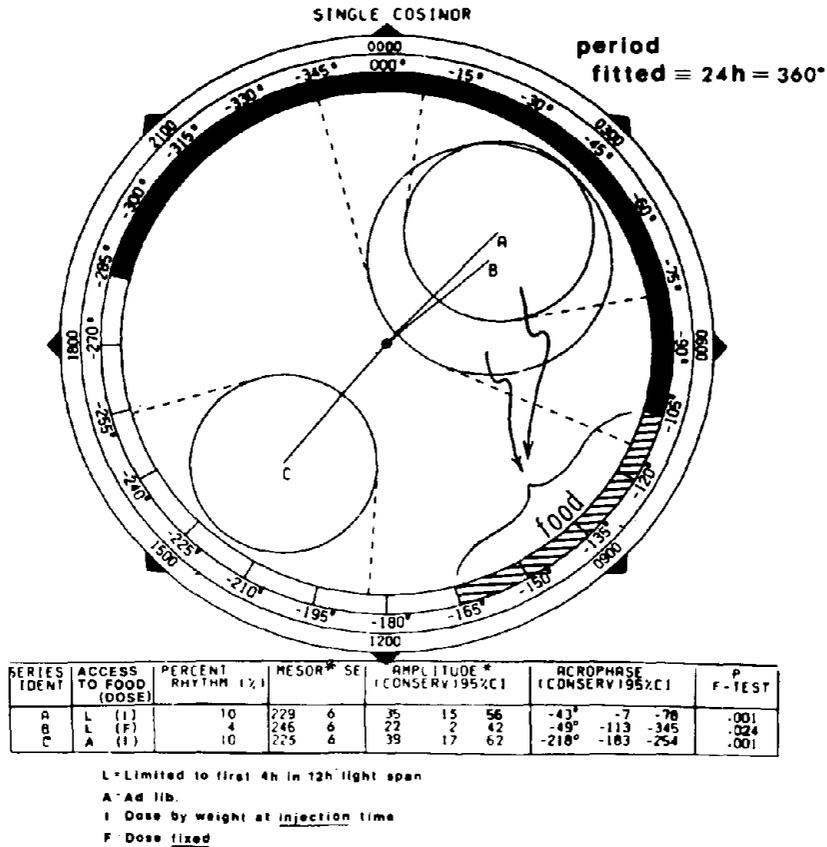


Figure 19. Rats feeding ad libitum or trained to eat only during single two-hour span daily (in the early part of 12-hour light span) were inoculated subcutaneously with immunocytooma. Beginning three weeks later, separate subgroups of test animals were treated with adriamycin at one of six time-points during a 24-hour span. Survival time depended upon feeding schedule as well as upon the circadian timing of treatment.

lost weight, while, if the same amount of food was consumed as an evening meal, the subjects showed, on the average, either a statistically significantly



\*Mean survival time in hours after LD90

Figure 20. Two groups of mice (A and B) were trained to eat only during four-hour span in early light each day. Control group (C) had food continuously available. To examine circadian rhythms in susceptibility to adriamycin, a toxic dose of the drug was administered to separate subgroups at one of six timepoints during a 24-hour span. To compensate for changes in body weight due to food ingestion, animals of group B received fixed amount of drug, while mice in groups A and C received dose based on body weight. For each group data on survival time as a function of injection timing were fitted with 24-hour cosine curve to obtain estimates of circadian amplitude and acrophase. These parameters are depicted as length and direction, respectively, of vector originating at center. Circles at tip of each vector indicate 95% confidence regions for parameters.

small loss or else a gain in weight. Moreover, this observation was extended to volunteers on a limited free choice diet, unrestricted in amount but with restricted temporal availability.<sup>20, 32</sup>

#### 7. Endocrine aspects of meal-timing.

The internal timing of circadian rhythms in human blood hormones influencing the fate of a meal is also altered by meal-timing. Circadian rhythms in plasma insulin and glucagon, on the one hand, and adrenal corticosteroid hormones, on the other hand, were differently timed in relation to each other as well as to the 24-hour living routine, on a regimen of 2000 calories, consumed as “breakfast only” as compared to 2000 calories eaten as “dinner only.”<sup>14</sup>

#### 8. Meal timing and the shift worker.

Such results complement casual statements that an animal’s utilization of food consumed will depend to some extent on the “time of day.”<sup>64</sup> Meal timing seems to alter the actual timing and other relations of certain mammalian rhythms at levels ranging from the cell to the entire organism. Such results need extension at all these levels and must also be complemented by work covering the entire life span.

Those adhering to a homeostatic hypothesis mistakenly regard our eating schedules as phenomena dictated by no more than hunger and satiety, convenience, social habits and pressures. The alternate view, based on fact rather than fancy, admits of rhythmical processes in spontaneous food intake as well as utilization. Feeding behavior is related in substantial part to the organism’s temporal structure, rather than solely to environmental factors, as demonstrated in several kinds of studies, some with food available constantly in time, quality and quantity,<sup>9, 10, 11, 29, 52, 58</sup> others weighing the relative importance of the time elapsed since the last meal, on the one hand, and circadian state on the other hand.<sup>7</sup>

From the viewpoint of chronodietetics<sup>31</sup> the timing of meal(s) can be considered as an important synchronizing factor when the availability of food is restricted to a few hours, with a specified location along the 24-hour scale. Since the timing of a meal or meals proves to have important effects on the body in health and disease, one should support the proposition that optimal nutrition requires a consideration of *when* food is consumed. Being able to obtain “more for less” in this way will have important implications in a world of ever-increasing shortages. From the viewpoint of occupational health and safety the possibility of shifting rhythms in performance [and in factors underlying it<sup>21</sup>] to optimize productivity and health is as important as is rhythm manipulation for augmenting the efficacy and safety of treating disease (notably the chemotherapy of cancer).

How a regular meal might best be timed — just before the start of the daily work span or at some other time — may depend on (a) the par-

ticular schedule (e.g., fixed schedule work or rotating shifts at intervals of several days or more); (b) the stage in a particular schedule — e.g., night-time versus day-time work (for a worker on, say, a rotating shift); and on (c) characteristics of the worker, e.g., lark, owl<sup>19, 57</sup> or other. The optimization of meal times for the shift worker etc. may be sought in the context of whether the timing of a meal facilitates the actual shift of certain rhythms (but not of others) and whether, under certain circumstances, this rhythm-shift is desirable from a physio-psycho-social viewpoint. Controlled access to food can, in fact, be made either to oppose or to augment effects of synchronization by the lighting regimen on circadian rhythms of mice,<sup>44</sup> Figure 14.

When routine shifts have to be repeated at relatively very short intervals, one may manipulate meal times in the endeavor to maintain the status quo rather than to facilitate rhythm shifts to conform with “new” schedules of only short duration. One then prefers meals timed to decelerate the shift-rate.

#### 9. When to “delay” and whether to “advance” schedules.

Much controversy about the effects of shift work could be the result of a lack of attention to the direction of a shift in work schedules, i.e., to the known polarity in the rate of human shifts and more broadly of shifts in circadian rhythms for any and all forms of life examined from this viewpoint. In response to a change in the temporal placement along the 24-hour scale of a regimen of light for 12 hours alternating with 12 hours of darkness most organisms adjust more rapidly if a schedule is shifted by delaying rather than advancing subsequent events on the schedule, Figures 16 and 17. This experience corresponds to that of most human beings. For example, following transmeridian flight the majority of individuals adjust more rapidly after a flight from east to west than vice versa.

This polarity could be exploited in the selection of an individual for shift work and in the kinds of shifts to which he may be subjected. It may be worthwhile designing tests to find out the direction in which a given person adjusts faster so that a compatible shift work schedule can be devised.

As another aspect of optimization of shift work, one may also select for such work those who by virtue of their circadian system structure are likely to become more efficient and healthy (as well as safe) shift workers. One has to develop a test battery to ascertain this circumstance, against the background of parallel studies of mice and human beings. Tests of productivity, efficiency, ratings of well being and assessment of adjustability of rhythms are overdue. One may have to individualize recommendations for shift work and even for work on a regular schedule. If an individual on a fixed 24-hour schedule runs with some hormonal and/or other rhythms on a 25-hour cycle, he may gradually accumulate

debts because he would be required to shorten his "natural" cycle by one hour each day.

On the other hand, such a person may adjust more readily to a *delaying* shift of his work schedule (e.g., the lengthening of a single work or rest span) than would a subject whose free-running period was, say, 23 hours. The latter subject may, however, accommodate easily to an *advancing* shift of his work schedule.

Such a relationship between free-running periods and rate of rhythm-shifting also has been examined in laboratory animals and human beings, as reviewed by Aschoff.<sup>3,4</sup> Studies comparing the effects of advancing and delaying shifts on lifespan also have been done by Aschoff and by Hayes; such investigations are more readily done on insects with short lifespans. However, they have to be interpreted with due regard for species differences in, among other factors,<sup>3,5</sup> poikilothermy versus "homoiothermy" and metabolic rate.

#### *Conclusion.*

The test of circadian system adjustability is overdue and feasible for mice and human beings with available designs, instrumentation and methods of analysis. Already, sufficient evidence from experimental animals demonstrates that the age at which schedule changes simulating shift work are initiated plays a critical role with respect on lifespan.

To follow up on various basic findings on experimental animals for an optimization of scheduling human shift work is immediately practical and should be the goal of continuing parallel studies on human beings (on productivity and health) and experimental animals (on overall resistance and lifespan).

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**SURVIVAL OF THE CODLING MOTH, THE  
PINK BOLLWORM, AND THE TOBACCO BUD-  
WORM AFTER 90° PHASE-SHIFTS AT VARIED  
REGULAR INTERVALS THROUGHOUT THE  
LIFE SPAN**

*Dora K. Hayes\**

Sullivan et al (1969) demonstrated that manipulation of the photoperiod was harmful to the cockroach, *Leucophaea maderae* (Fabricius). However, manipulations such as phase-shifting are not always deleterious to an organism; as reported in this paper, one phase-shifting regimen prolonged the life span slightly. The studies reported here represent one aspect of the research conducted in our laboratory, that of developing information that could lead to specific control of insect pests with minimal damage to the environment and to users of agricultural products. We are interested in both the physical effects on insects of phase-shifting and other kinds of manipulations of light and/or temperature regimens and in the biochemical reactions involved in responses to environmental factors, such as light, that affect insect development (Hayes et al 1972, 1974, Schechter et al 1972).

*Materials and Methods.* We studied three species of insects, the codling moth, *Laspeyresia pomonella* (L.), the pink bollworm, *Pectinophora gossypiella* Saunders, a pest of cotton squares (buds), and the tobacco budworm, *Heliothis virescens* (F.), a pest of tobacco, cotton and possibly soybeans.

Apples containing 2-day-old codling moth larvae were placed in Biological Oxygen Demand (BOD) boxes in 1 gallon glass jars covered with surgical cotton and cheesecloth. When the larvae exited from the apples and pupated or spun up in diapause (hibernation), they were placed in polystyrene petri dishes and held until they emerged as adults and died. Time until death was recorded for each insect. The temperature in the boxes was maintained at  $25^{\circ}\text{C} \pm 1.5^{\circ}\text{C}$ ; relative humidity was close to 60%. Each box was equipped with one 15-watt cool-white fluorescent light tube; 24-hour timers were used to adjust time schedules.

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\*Co-authored by B. M. Cawley, F. Halberg, W. N. Sullivan, and M. S. Schechter of the University of Minnesota at Minneapolis.

The 90° phase advance was achieved by shortening the photophase to 6 hours every 3, 6, or 12 days; the 90° delay by lengthening the photophase to 18 hours every 3, 6, or 12 days. The 180°-shift was obtained by lengthening the photophase to 24 hours every 3 days.

*Results.* The results of the effects of phase-shifting on the codling moth larvae are shown in Table 1. Results are presented with larvae in diapause (hibernation) both included and excluded. The Chi-square test was used to determine whether values under each regimen in each test were significantly different from the control held throughout the test on LD<sub>12:12</sub>. Most of the regimens either had no effect or resulted in shortening of life; the 90° phase delay every 6 days, however, appeared to prolong life slightly in codling moth larvae. Data obtained in tests with the pink bollworm and the tobacco budworm were similar to those obtained with the codling moth (i.e., a trend toward improved survival was noted in the regimen in which the 90° delay was introduced every 6 days).

*Discussion.* We had anticipated the finding that some phase-shifting regimens would result in shortening of life; the slight, but significant prolongation of life above that of the controls in the tests in which the phase was delayed 90° every six days was an interesting finding. As a possible explanation we can suggest that when the tests were initiated, a basic photoperiodic regimen of LD<sub>12:12</sub> was chosen as the control condition; this regimen is one which induces diapause (hibernation) in susceptible members of the population. It is possible that the phase-shift which prolonged life did so by enhancing the effects of the LD<sub>12:12</sub> regimen in promoting (or inhibiting) reactions which would delay development slightly, but would not result in diapause. Actual diapause would not be induced, however, so that these insects would merely mature at a slower rate than the LD<sub>12:12</sub> controls.

The results presented in this paper suggest also that phase-shifts in insects need not necessarily result in earlier mortality than in animals not so treated, as was found by Aschoff (1971), but that depending upon the species and probably upon other environmental conditions as well, carefully selected photoperiodic regimens in which phase shifts are incorporated may actually prolong life.

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TABLE 1.

*Mortality in Codling Moth Adults After Phase-Shifting — Compared to Mortality of Non-Shifted Controls at 50% Mortality.*

| Regimen                  | Test no. | Total no. adults | % dead based on adults | p <sup>a</sup> | Total no. insects <sup>b</sup> | % dead based on total | p <sup>a</sup>     |
|--------------------------|----------|------------------|------------------------|----------------|--------------------------------|-----------------------|--------------------|
| Control                  | 1        | 28               | 50                     |                | 67                             | 21                    |                    |
|                          | 2        | 30               | 50                     |                | 57                             | 26                    |                    |
|                          | 3        | 38               | 50                     |                | 59                             | 32                    |                    |
| 90° advance every 3 days | 1        | 32               | 67                     | >0.1           | 79                             | 27                    | >0.1               |
|                          | 2        | 35               | 26                     | < .01          | 78                             | 12                    | < .01              |
|                          | 3        | 36               | 94                     | > .1           | 52                             | 65                    | < .01              |
| every 6 days             | 1        | 23               | 67                     | > .1           | 77                             | 20                    | > .1               |
|                          | 2        | 31               | 90                     | < .01          | 58                             | 48                    | < .01              |
|                          | 3        | 55               | 89                     | < .01          | 82                             | 60                    | < .01              |
| every 12 days            | 1        | 23               | 51                     | > .1           | 81                             | 15                    | > .1               |
|                          | 2        | 22               | 30                     | > .1           | 72                             | 8                     | < .01              |
|                          | 3        | 34               | 91                     | < .01          | 48                             | 65                    | < .01              |
| 90° delay every 3 days   | 1        | 27               | 86                     | > .1           | 64                             | 36                    | > .1               |
|                          | 2        | 29               | 81                     | < .01          | 64                             | 38                    | < .05              |
|                          | 3        | 44               | 84                     | < .01          | 61                             | 60                    | < .01              |
| every 6 days             | 1        | 22               | 44                     | > .1           | 84                             | 12                    | > .05              |
|                          | 2        | 16               | 21                     | < .05          | 63                             | 6                     | < .01              |
|                          | 3        | 27               | 30                     | < .05          | 45                             | 8                     | < .06 <sup>c</sup> |
| every 12 days            | 1        | 32               | 84                     | < .01          | 66                             | 41                    | < .01              |
|                          | 2        | 35               | 63                     | > .2           | 71                             | 41                    | > .3               |
|                          | 3        | 43               | 90                     | < .01          | 51                             | 68                    | > .1               |
| 180° shift every 3 days  | 1        | 21               | 81                     | < .01          | 71                             | 24                    | > .1               |
|                          | 2        | 29               | 64                     | > .1           | 56                             | 32                    | > .1               |
|                          | 3        | 41               | 68                     | < .02          | 54                             | 52                    | < .02              |

<sup>a</sup>p calculated using Chi-square test that difference from control could have occurred by chance alone.

<sup>b</sup>Adults plus larvae in diapause.

<sup>c</sup>Graphically interpolated:  $\chi^2$  for p < 0.05 = 3.84  
 $\chi^2$  for this test = 3.73

## CIRCADIAN RHYTHMS: DISCUSSION

*Elliot D. Weitzman*

It is a pleasure to discuss these two papers. Dr. Halberg is one of the world leaders in biological rhythms, and coined the term "circadian" in 1959. As has been emphasized, the study of these rhythms is critical to human beings who have to function on differing schedules in relation to their 24-hour sleep-wake and other physiological functions.

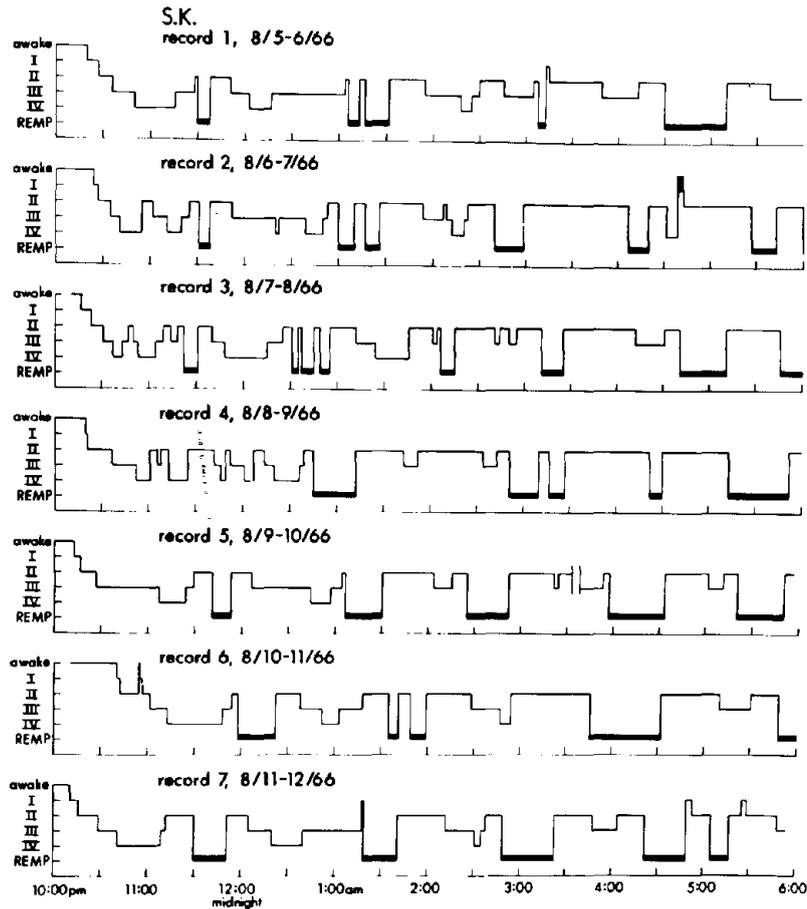
Because of time limitations, I should like to confine my remarks in this discussion to the significance of shifts of the 24-hour sleep-wake cycle in man, both in a laboratory situation and in a real-life work situation.

Our group's general approach has been to make detailed sequential 24-hour observations and measurements on limited numbers of subjects at frequent intervals from several hours for body temperature, to 20 minutes for alertness and hormones, down to one minute for sleep stages. These measures are then correlated in time in relation to conditions which may be imposed by us in the laboratory or by an employer in the case of shift workers. The other approach to analyze the psychological and physiological effects of shift work, of course, is a survey of large numbers of persons with varying sleep-wake habits and other characteristics of shift workers.

Figure 1 illustrates how most normal people sleep at night (at least those of us who are under 50). This is a normal subject who slept in the laboratory every night for a period of seven nights. His waking time is almost zero. He goes to sleep quite rapidly and stays asleep with an occasional brief awakening in the latter part of the night. The most important features are the complexity and organization of the sleep stages. There is a period of what we call non-REM sleep (Stages I-IV) for the first few hours of the night, followed by an alternating sequence of REM and non-REM stages as the night goes on.

The dark lines are the REM periods and the light lines are the non-REM periods (wakefulness is at the top). This is normal, healthy sleep. The pattern is complex but reasonably predictable and quantitative.

Figure 2 shows how we secrete cortisol and growth hormone on a 24-hour basis. The spiking, peaking curve is the way we all secrete



*Figure 1. Normal sleep pattern*

cortisol every day. It is not a smooth curve, but rather a complex, episodic pattern of secretion. There are periods of the day in which we secrete large amounts of the hormone, but always in discrete, episodic bursts. The growth hormone pattern, on the bottom of the graph, illustrates how the normal person secretes this hormone every day.

We have to take these kinds of patterns into account when we talk about what happens to man when we shift him around on various work schedules. We cannot just take infrequent samples, and we cannot just assume that relatively simple mathematical functions apply.

Figure 3 illustrates what happens to some of these functions when

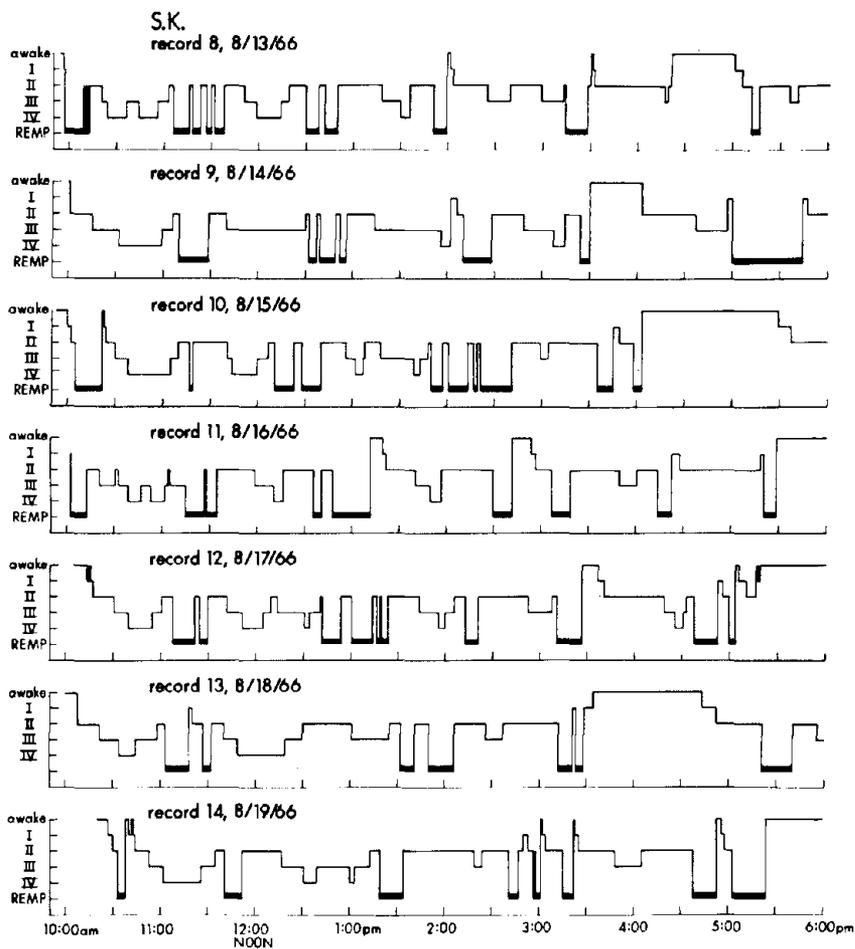


Figure 2. Twenty-four hour cortisol and growth hormone secretion

the sleep-wake cycle of a normal subject is acutely shifted by  $180^\circ$  in the laboratory. This is a strictly controlled experimental situation. First, the subject goes to bed at 11 at night and gets out of bed at 7 in the morning. Then he is shifted by going to bed at 11 in the morning and remaining in bed until 7 in the evening. What happens to the sleep patterns? In my review of the literature, I am impressed that the most significant complaint when human beings are shifted in an industrial situation is a disturbance of their sleep patterns. It is the most universal complaint in their own daily lives as well as in their family and other social relationships. During the first week after such an acute sleep-wake

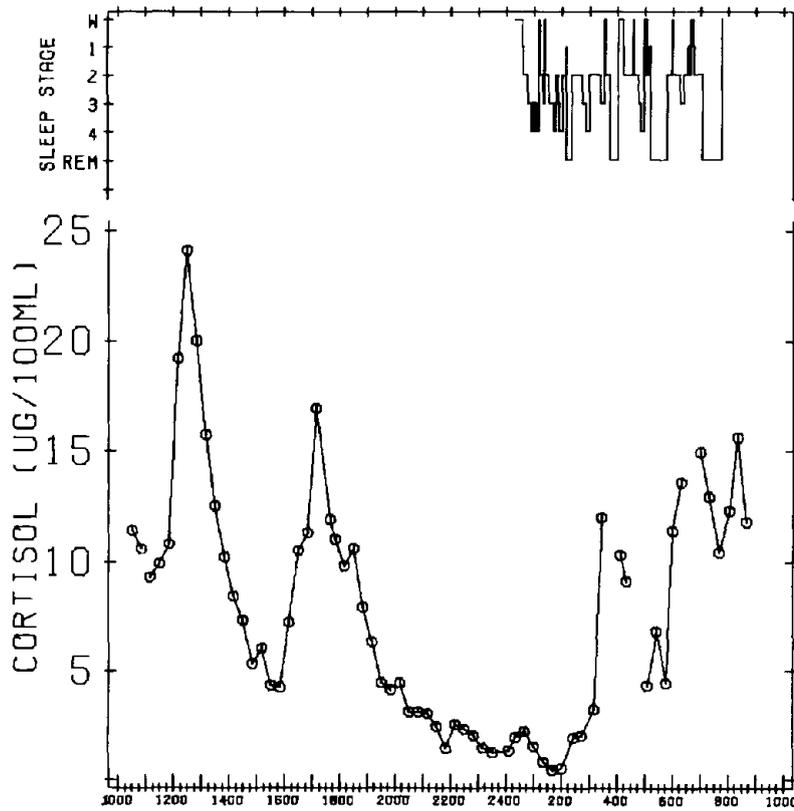


Figure 3. Cortisol excretion pattern after 180°-shift of sleep-wake cycle in a normal subject.

reversal there are some very clear changes in the sleep pattern. Sleep is much more disrupted by frequent awakenings, particularly towards the end of the daytime sleep period. There is also an alteration of the normal REM non-REM pattern of sleep stages. This persisted into the second week of the study. It did not just go away in two or three days, even though the subject had plenty of opportunity to sleep for eight hours in a comfortable bed in a darkened, quiet room.

For the first and second week after inversion of the sleep-wake cycle, then, four out of a group of five normal subjects could not remain asleep. They became sleep deprived even though they had plenty of opportunity for sleep. This has been a very consistent finding. In a

second and longer study of a similar reversal of the sleep-wake cycle we have found that it takes a period of one to two weeks for reversal to accommodate a normal night's sleep.

What happens to other measured variables? What happens to the adreno-corticoid hormones and what happens to our body temperature pattern? Dr. Halberg has shown clearly that there is a period of time when, even though we are theoretically shifted, there is a delay in the adaptation of many physiological systems. In this situation, we also have found that body temperature, even during the second week of such a shift, did not adapt. We have found, in a longer nine-week reversal study (three weeks sleeping at night, three weeks sleeping during the day and then three weeks sleeping at night) that the body temperature indeed did invert when the sleep-wake cycle inverted but that it took somewhere between the second and third week for this to occur. The inversion of the body temperature curve is not just a shift of acrophase but is a complex multi-pattern change that occurs during the course of the transient phase of adaptation to the 180°-shift.

Finally, we are currently studying a real-life work situation: the effects of shift work on nurses in our hospital in New York. We are measuring sleep stage pattern, body temperature, hormonal patterns, as well as subjective assessments of sleep, work performance and general well-being. Thus far, in the small group of nurses we have studied, all have demonstrated major disruptions of their sleep patterns even more severe than the disruptions shown by the normal subjects under controlled laboratory conditions. The sleep pattern changes in night shift workers from a sustained six to eight hour sleep period into a series of fragmented nap-like episodes during the daytime. This fragmentation is accompanied by a major deprivation of sleep, the sleep time decreasing by 50-60% in these working nurses.

Figure 4 shows a nurse who has been on a shift work schedule for 10 years during which she characteristically works on the night shift for five days of every week. On weekends, she reverts to a more socially acceptable pattern of nocturnal sleep and diurnal waking. This reversion on weekends is typical of shift workers who otherwise maintain a reversed sleep-wake pattern. This nurse always goes back and forth, every week, even though she has been a "night worker" for 10 years. The pattern of the sleep stages is shown separately for REM (black in the upper panel) and non-REM stages 3 and 4 (black in the lower panel, with the remaining stages shown in gray). Not only is the sleep period fragmented by long awakenings, but the normal organization of the stages has been lost. For example, the time spent in stages 3 and 4 sleep is no longer concentrated at the beginning of the sleep period as is the case in normals, and in subjects who have been acutely phase-shifted or sleep deprived.

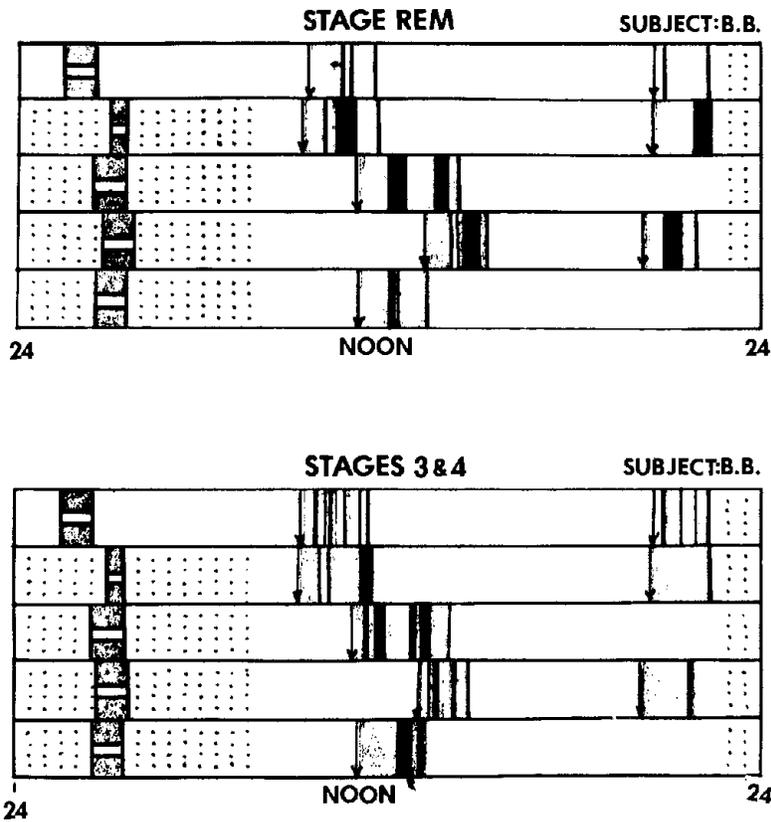


Figure 4. Sleep pattern of a hospital nurse and chronic shift work experience.

We don't know what the significance is of this disturbed pattern for performance and health, but it is clear that the sleep pattern is very different from the way people normally sleep. In addition to the above disturbance, several of our studied nurses take a daytime nap during working hours (represented by the stippled areas in Figure 4). This may be common, at least in our observations, of hospital night shift workers.

There is little question that the effects of shift work on various physiological functions, especially the sleep-wake system, are major. This is an important area for further discussion and study in terms of the behavioral, social, and psychological significance of biological rhythms in relation to industrial shift work problems.

## HEALTH AND WORK SHIFTS\*

*Howard Levine*

The evaluation of the effects of shift work on health is made more difficult by the lack of quantification of health in terms other than "absence of illness."

The term "shift work" includes a variety of arrangements such as double-day shifts, stabilized day or night shifts, rotating or flexible shifts, and even part-time evening work. Hence, the difficulty in clearly defining the influence of shift work on health and the great need to learn about inter and intra individual differences to adapt to the variety of shift systems. As suggested by Halberg<sup>7</sup> the provision of a health summary form based on chronobiology would provide more precise information and quantification of health, particularly if it is introduced earlier in life.

Extensive reviews on shift work have been written by Bjerner, Holm, and Swenson<sup>2</sup> as well as by Menzel<sup>18</sup>. Bruusgard<sup>3</sup> estimated that about 20% of the worker population is unable to adapt to shift work. Taylor<sup>31</sup> concludes there is little evidence that shift work continued for any length of time significantly affects health either in terms of sickness, absence or mortality; however, only those who remained on shift work have been studied.

Wilkinson and Edwards<sup>37</sup> found that adaptation was more acceptable in fixed rather than rotating shifts. On the other hand, Walker<sup>34</sup> suggests that frequent alternation of shifts on continuous work was preferred by the workers to the commonly used one-week spells due to reduced experience of "fatigue and monotony." Oginski<sup>20</sup> and Wild and Thcis<sup>36</sup> indicated that the 7-15-23 system is better than 6-14-22. Saito<sup>27</sup> suggested that shifts in the order of night, evening and day instead of the more common day, evening, night pattern were advisable.

McGirr<sup>17</sup> considered conditions that would preclude employees from alternating shift work as (1) a need for continuous medical therapy as in diabetes or epilepsy, (2) serious gastrointestinal diseases, such as

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ulcer and colitis, (3) heart and circulatory diseases, and (4) marked anxiety syndromes.

Aanosen<sup>1</sup> on finding that many of the workers who transferred to non-shift work for medical reasons were "early to bed—early to rise," suggested that further studies be done on patterns of sleep and sleep types to establish criteria for selection of shift workers. Hääkinen's<sup>5</sup> study of well adapted shift workers showed significantly less psychosomatic tension than his poorly adapted group.

Kleitman<sup>11</sup> called attention to "morning" and "evening" types of individuals. Pátka<sup>23</sup> noted significant differences of alertness, performance and adrenal secretion in the "morning workers" as compared to the "evening workers." She found in a group of female habitual morning workers far more introversion than in the evening workers. In a study of circadian rhythms of food intake and oral temperature in "morning" and "evening" types identified by means of a questionnaire Ostberg<sup>21</sup> estimated that morning types are approximately 1 $\frac{3}{4}$  hours earlier than their evening counterparts in starting and finishing their meals, and the maxima of temperature between the groups are separated with values at 1457 and 1743 hours for the morning and evening group respectively.

Voigt, Engel and Klein<sup>33</sup> showed a circadian rhythm of heart rate for fixed loads in bicycle ergometer tests. Ostberg<sup>22</sup> exercised subjects with a standard load at different time points. The morning group subjects were least fit during the beginning of the night shift, the evening subjects were least fit during the beginning of the morning shift, and the middle group subjects were affected in an intermediate way. He also found that the morning type slept best on the morning shift week and the evening type slept best on the evening shift week. Klein<sup>10</sup> states that true physical fitness can be evaluated properly only by a maximal exercise test. He feels that by using indirect fitness tests to evaluate day/night variations, the differences of fitness indices and not fitness itself are being measured. All indirect fitness tests are based on the fact that subjects with a higher performance capability of physical exercise (for example, trained people) have lower heart levels both at rest and during exercise; consequently, on such tests lower heart rates are scored better if measured under the same experimental conditions.

Tune<sup>32</sup> studied 52 shift workers and recorded their hours of sleep and wakefulness for a period of 10 weeks. Compared with matched non-shift working control subjects it was found that they had higher average durations of sleep per 24 hours and more long naps outside the major sleep period. A comparison of the on and off duty records from the shift workers shows that a sleep debt was incurred during the former which was largely paid off by taking long naps in the latter.

Weitzman et al<sup>85</sup> studied five healthy young men subjected to an acute sleep/wake cycle reversal of 180° (12 hours) in the laboratory. These subjects slept one week at night (10 p.m. to 6 a.m.) followed by two weeks of day sleep (10 a.m. to 6 p.m.) A significant increase in waking and a decrease in REM sleep time occurred during the inverted sleep period. At the reversal there was a shift of REM and stage 2 sleep towards the early part of the sleep period and waking shifted to the latter part. The duration of episodes of all stages of sleep decreased and a number of changes of sleep stage increased after reversal.

Despite these changes, duration, amount and stability of sleep stages, the basic 90 to 100-minute cycling was preserved following reversion to day sleep. They emphasized the importance of polygraphic definition of sleep stages and studies of circadian cycle shifts. The similarities of depression to inverted sleep/wake cycle raised the question of whether some of the physiologic and psychologic changes associated with endogenous depression could be secondary to the disturbed phase shifted circadian cycle.

Menzel<sup>18</sup>; Bjerner, Holm and Swensson<sup>2</sup>; and Propkop<sup>24</sup> showed that in the frequency of car accidents in which drivers fell asleep at the wheel, a strong second maximum is present in the early afternoon, the first maximum appearing 12 hours beforehand.

Hildebrandt, Rohmert and Rutenfranz<sup>9</sup> studied the frequency of errors made by locomotive drivers of the federal German railway and concluded that fatigue is able to evoke a 12-hour period of vigilance functions superimposed on the normal circadian period. The possibility of fatigue/food synchronizing an underlying shorter ultradian period exists.

Kleitman<sup>11</sup> commented upon the relationship of variation of psychometric performance tests with body temperature. Industrial workers tested by Colquhoun and co-workers<sup>4</sup> for vigilance and quick arithmetic performance while on different shift systems of four, eight or 12 hours in general were subjects whose temperature rhythms adjusted quickly to a new shift and showed a similar adaptation in performance rhythms.

Mills<sup>19</sup> cautions that parallelism does not imply relationship. Rutenfranz, Aschoff and Mann<sup>26</sup> conclude that both body temperature and reaction time exhibit circadian rhythms which appear to depend on each other only because of their simultaneous control by Zeitgebers. There is no support for the hypothesis that reaction time and body temperature are causally related.

Aschoff believes that any attempt to shorten the duration of re-entrainment after shifts or to reduce the loss in efficiency during this time would depend on a deeper understanding of the underlying circadian mechanism. Shifts of artificial light/dark cycles by six hours in human

subjects kept in isolation in an underground bunker exposed to artificial light/dark cycles as synchronizers were followed by activity cycles of the subjects rather immediately; the rhythms of body temperature, however, did not regain their normal phases until several days had elapsed.

Association between rhythms may be studied not only in people shifting from day to night work or vice versa but also by deliberately altering their clock time when living in isolation in an arctic summer, by staying underground or by flying through different time zones. The arctic summer gives an opportunity to provide a non-24-hour routine.<sup>28, 29, 30</sup> Simpson and Bohlen<sup>28</sup> studied the effect of living on a 21-hour day upon the circadian rhythms in output of 17-hydroxycorticoid steroids and other urinary electrolytes. Although food intake, as well as activities in sleep/wakefulness, were strictly maintained on a 21-hour day, these rhythms were not synchronized by this particular odd routine.

The phase-shifting of circadian rhythms permits an understanding of the underlying temporal organization along the 24-hour scale whether performed with or without geographic displacement. During a one-month study at the National Institutes of Health a phase-shift routine by 12 hours took place.<sup>15</sup> The study was divided into three parts — a span of high sodium intake of 240 mEq per day for 10 days and a span of low sodium intake of 9 mEq/day for 20 days. Urine was collected in four-hour spans for the entire 30 days and analyzed for electrolytes, 17-hydroxycorticoid steroids, and aldosterone. On seven separate days venous blood was collected every four hours and analyzed for similar constituents and for plasma activity. Stools were collected daily in four-day spans and analyzed for sodium, potassium, calcium, phosphorous and magnesium. Saliva was collected 5 to 11 times daily. Self-measurements of blood pressure and other physiological as well as physical and mental performance variables as described in the *Physiology Teacher*,<sup>8</sup> were made nine times daily. Blood pressure was also recorded automatically during the 30-day study every 10 minutes continuously during the day and night during each of the 24 to 48 hour spans totaling seven days.

During the entire study the patient ate a constant metabolic diet, stayed within an air-conditioned environment and had a definite set routine which he followed every day and maintained after the 12-hour phase shift. The acrophase for urinary volume, magnesium, calcium and phosphorous seemed to advance but the acrophase of potassium, 17-hydroxycorticoid steroids, chlorides and blood pressure apparently retarded. After eight days, most had not fully shifted, Figure 1.

The effect of round trip intercontinental flights also was studied by autorhythmometry with results shown for grip strength and eye hand skill.<sup>13</sup> These were prepared by fitting 24-hour cosine functions to

consecutive 20-day intervals displaced by one-day increments. The 20-day interval corresponds roughly to the total duration of the stay in Europe during the first continental flight. The right hand grip strength, Figure 2, shows that, on the average, the values abroad are below those

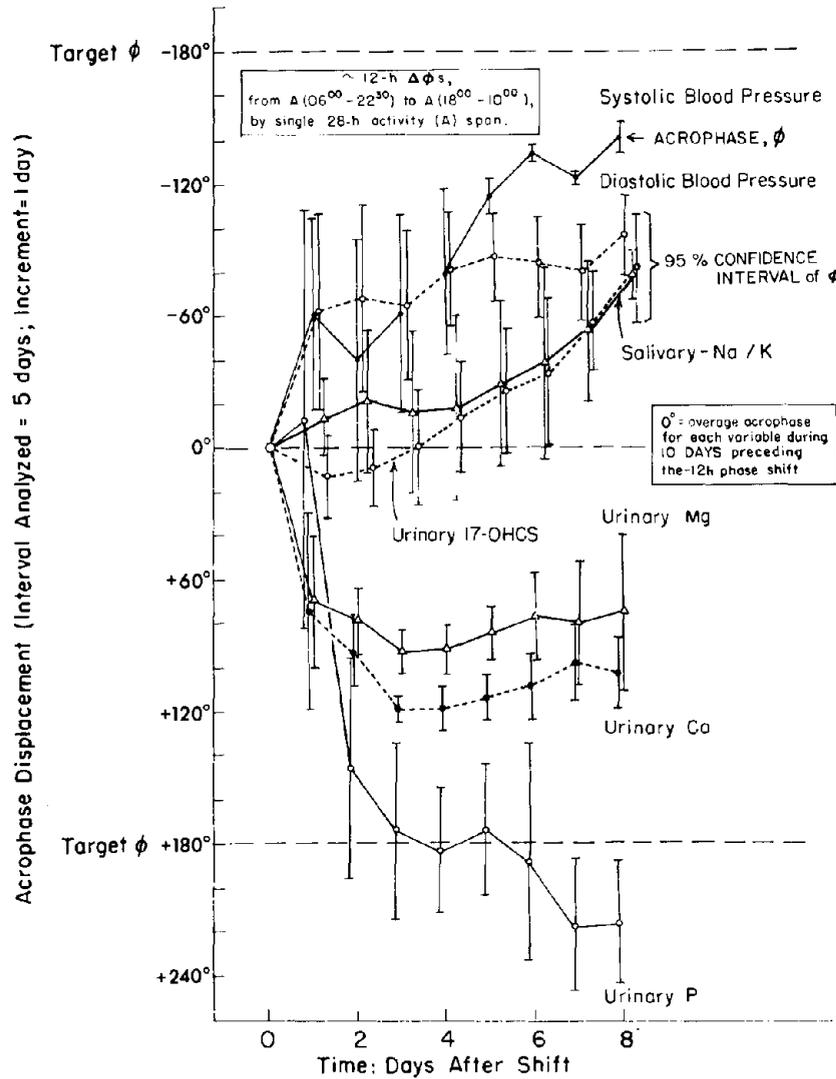


Figure 1. Differences in direction and extent of phase-shift among different circadian rhythms in response to a 12-hour delaying-shift of synchronizer ( $-180^\circ \Delta\phi$ s)\*. Results from self-measurements by a 57-year-old man.

obtained in Connecticut before and after this flight. A gradual adjustment of this rhythm to the six-hour difference in timing required by social schedules in Italy is apparent in the acrophases.

There is relative disadvantage in performance after arrival in Italy and awhile thereafter. There is a distinct drop in mesor and amplitude of the grip strength after the flight from west to east, but not after the return flight to Connecticut. The overall rising trend in hand grip mesor before the flight is confounded by multiple effects of learning, training, drug administration and perhaps the contribution of a circannual rhythm. The eye hand coordination, Figure 3, shows a marked deficit after the west to

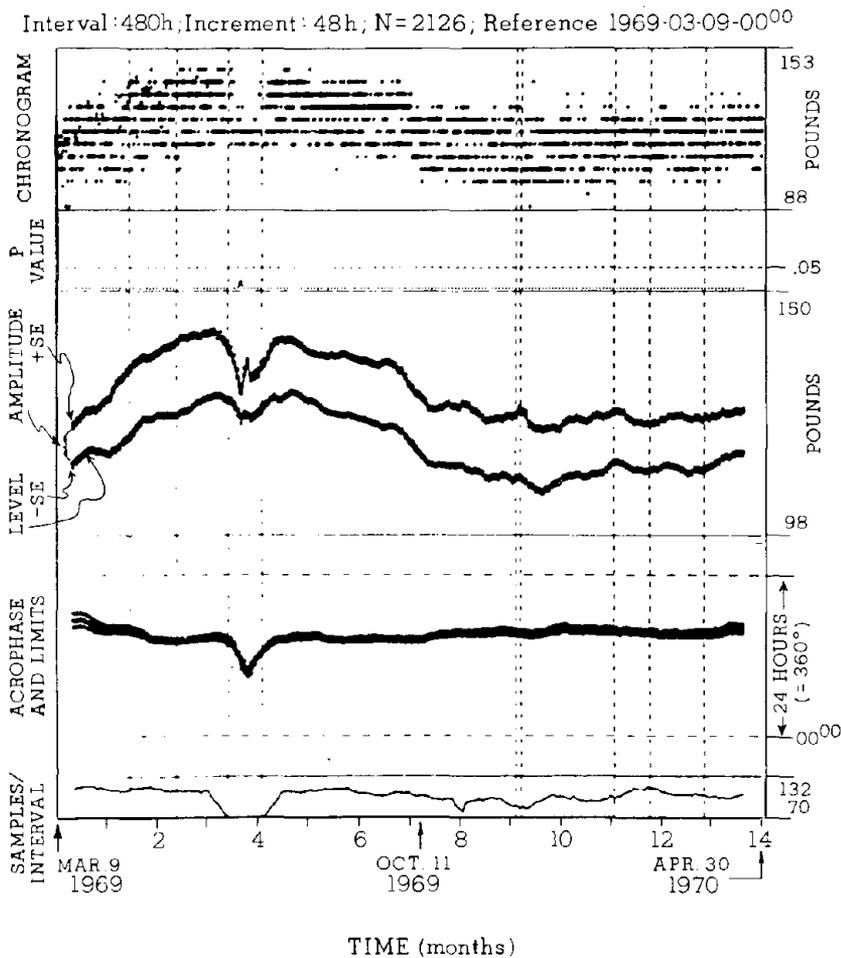


Figure 2. Grip strength, right hand, HL, mildly hypertensive physician

east flight. The rhythm adaptation following a flight from east to west involving social synchronizer delay seems to be faster than that following a flight from west to east involving synchronizer advance, despite the circumstance that rhythm advance is associated with the individual's returning to a familiar home setting, Figure 4.

The self-measurement, termed autorhythmometry, offers at low cost an increased data base descriptive of the subject in his habitual environment. It provides individualized ranges of usual values and estimates of rhythm characteristics not available with single timepoint sampling. The increased amount of individual data will aid in defining more precisely individual ranges of normalcy of many physiological variables. The

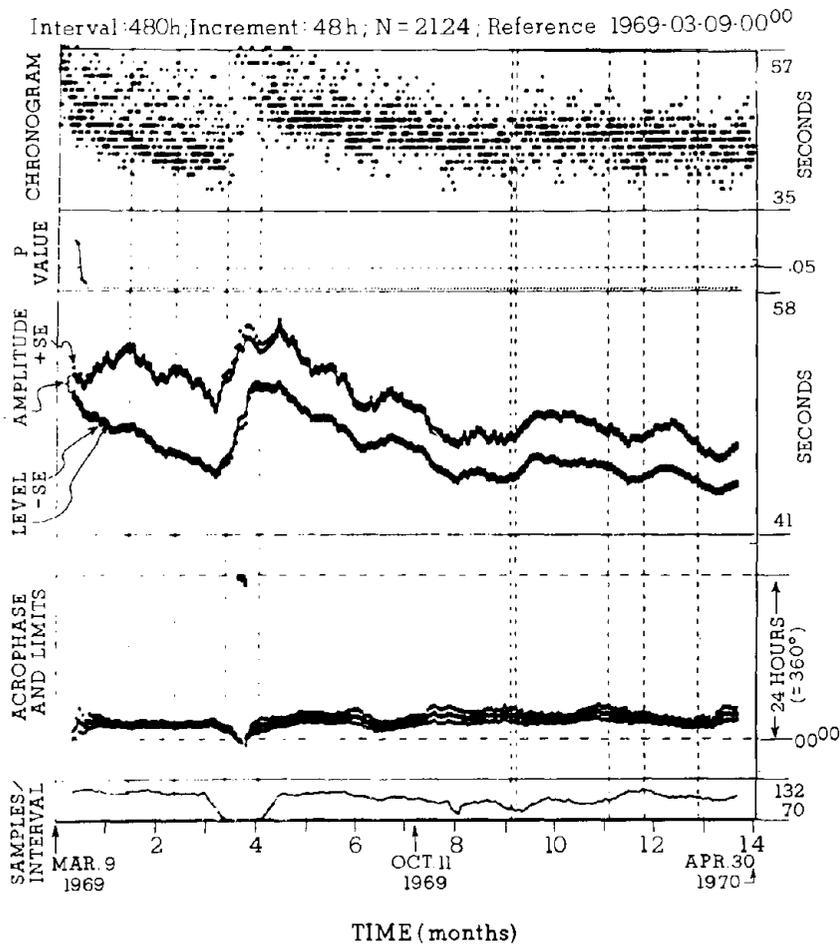


Figure 3. Eye-hand skill, mildly hypertensive physician

subject thus has an active role.

There is potential educational and therapeutic value from feedback of information. The risk of creating anxiety is small when the subject is properly informed and when the overly reactive individual is either "delabeled" or does not participate in self-measurements. The concept of timing for diagnosis and treatment is as fundamental in clinical medicine as the need to introduce a challenge or load for the diabetic who may have a normal fasting blood sugar or the patient with coronary artery disease who has a normal electrocardiogram.

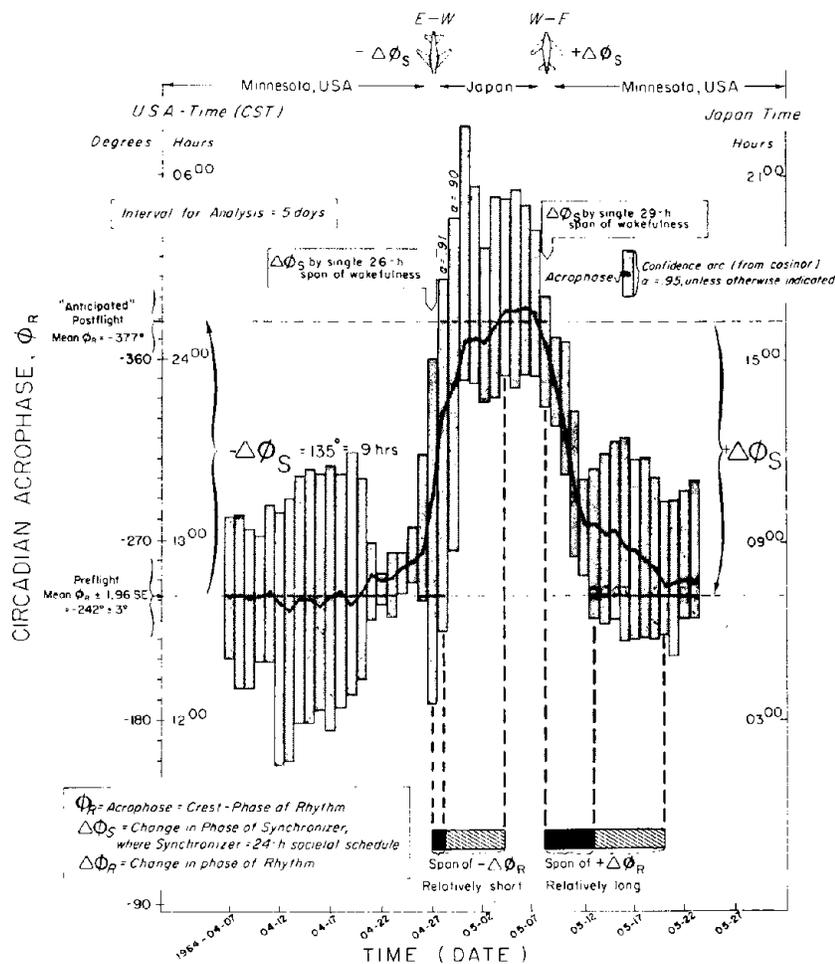


Figure 4. Phase-shifting of circadian rhythm in oral temperatures of five healthy adult white males.

The intraindividual variations of physiological functions emphasizes the need to individualize measurements. Children of the same age and sex may have variations of blood pressure so great that one's lowest systolic blood pressure is higher than a cohort's highest.<sup>10</sup>

Reinberg and Halberg<sup>25</sup> have emphasized the need to give drugs at the time of maximum effectiveness and minimal toxicity. We have studied the diuretic effects of chlorothiazide on healthy men depending on the time of administration.<sup>12</sup> They received U.S. Army "C" rations supplemented with salt and potassium chloride and containing a known amount of calories, water, sodium, potassium, calcium and iron. In a double blind study, 12 healthy men were divided into six groups of two each and given two tablets of either a placebo or 0.5 gram chlorothiazide every four hours for two weeks while collecting urine at the same time points. During the first four days only placebos were given. On the next four days chlorothiazide was thus administered to two subjects at 0200 to another at 0600 and so on at four hourly intervals; placebos were given at each of the other four hourly times. The subjects were their own controls. The drug had its most pronounced diuretic effect on subjects who received it at 1000, Figure 5.

In an overview we must consider the importance of relative timing for logistics and performance, Figure 6. We have the inter-relationships of the individual, the psychosocioeconomical factors of the family, the institution and the environment. Within this structure, performance and production are closely integrated with health, biological rhythms, and work shifts. The individual's goal of maximum health and minimum illness is linked with the institution's desire for maximum production and minimum cost.

### *Conclusion*

Information on the effects of shift work is confusing and contradictory. Is it an advantage or disadvantage? We need to quantify health, define illness, and collect and analyze data more precisely. Rhythmic variables should be evaluated not only for health assessment but also to adjust the kind and timing of treatment according to their characteristics.<sup>14</sup> There are available chronobiologic methods for objectively quantifying the effect of work-shift on health.<sup>6</sup>

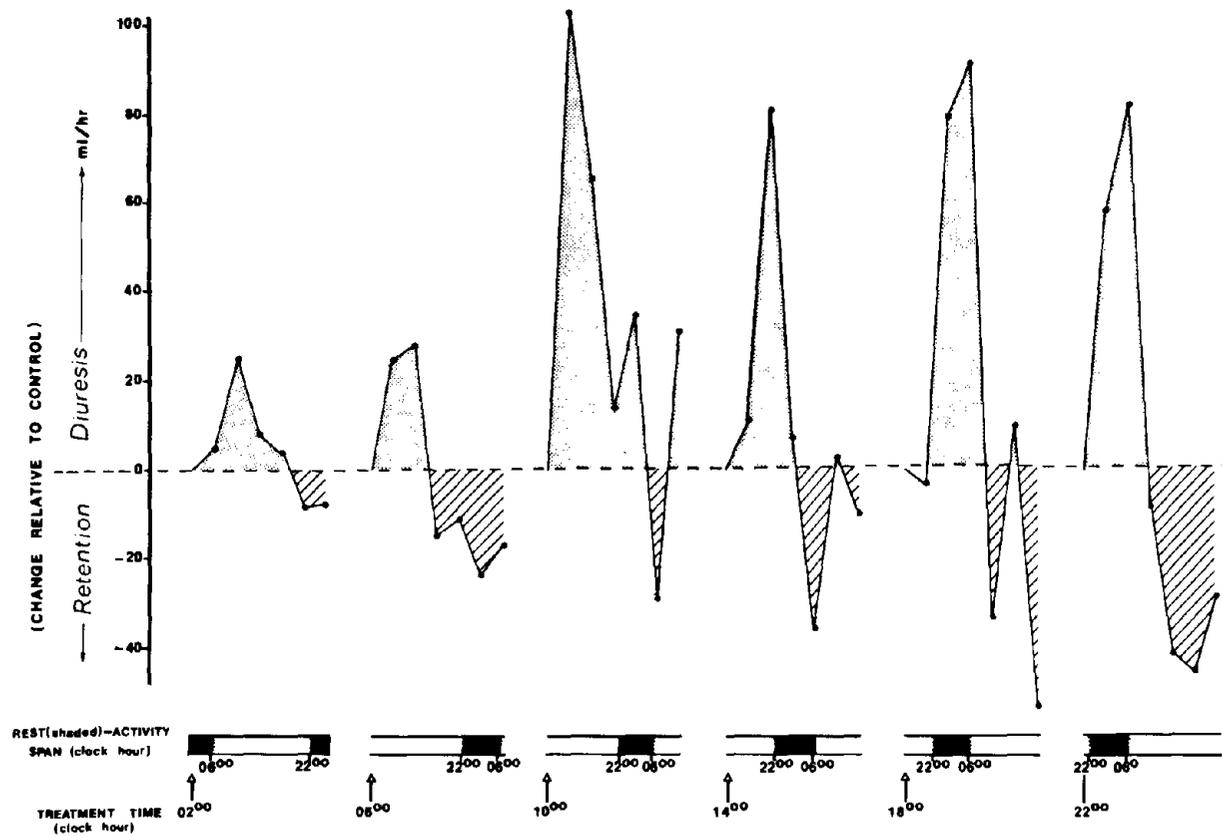


Figure 5. Time-course and extent of diuresis induced by chlorothiazide at different circadian stages in clinically healthy men.

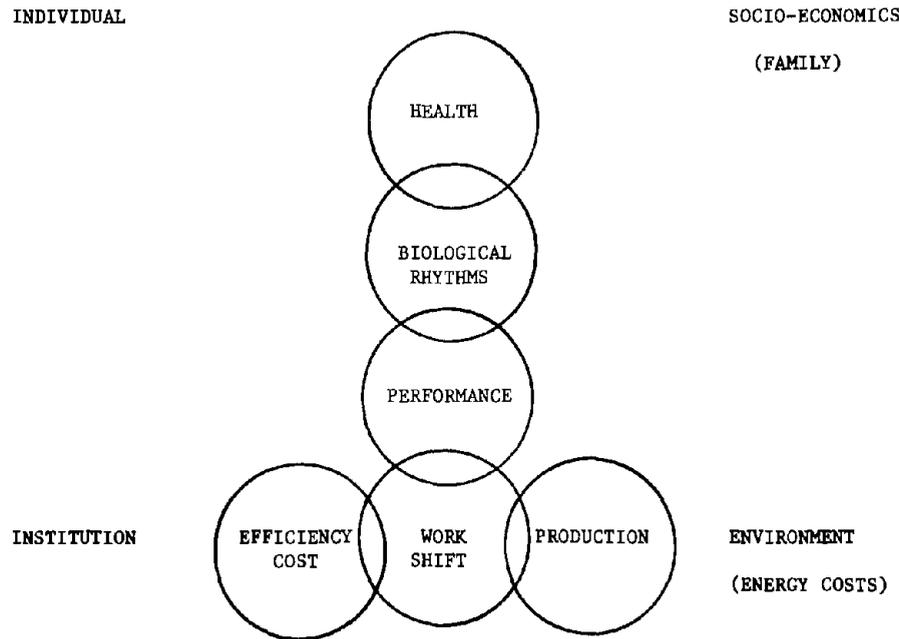


Figure 6. Relative timing for logistics and performance

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## HEALTH AND WORK SHIFTS: DISCUSSION I

*Joseph G. Bohlen*

Dr. Levine has raised a number of important points which deserve discussion. Let me focus on the prospects of chemically inducing more rapid phase-shifting.

In 1971, Dr. Hugh Simpson and I conducted a field trial of a Merck compound, Quiadon®, for possible chronobiotic effects.<sup>1</sup> The continuous daylight of arctic midsummer provides a unique opportunity for studying the physiological and psychological effects of a static phase-shift. For a three-week span in midsummer on an island in northwestern Greenland we collected and analyzed data from 12 subjects (nine Scottish medical students and three lecturers). Eight days were spent living a standardized eating, sleeping and activity routine on British Standard Time. This was immediately followed by an eight-hour delay, simulating a work schedule shift or a flight westward over eight time zones. Data collection continued for another 14 days. The variables studied were urine temperature, urinary sodium and potassium, eye-hand coordination and hand-grip strength, many of those variables discussed by Dr. Levine. The quality of sleep also was evaluated.

The pertinent action of Quiadon® is 5-hydroxytryptamine depletion. The 5-HT rhythm which normally is lowest during midsleep in diurnally-active individuals might perhaps be “driven” by ingestion of this compound prior to bedtime on each night following the phase-shift. This, theoretically, would accelerate readjustment to the new sleep-wake schedule. The additional action of Quiadon® as a tranquilizer might allay some of the anxiety of not being able to sleep soundly after a phase-shift. Drug allocation was double-blind with six subjects on active preparation and six on placebo.

In both drug and control groups, there was rapid resynchronization to the eight-hour phase delay. Yet some subjects adapted more rapidly than others. I don't think it was unique that in this case the older subjects (who were 20 years older than the nine medical students) adapted least rapidly, especially with rhythms in potassium excretion. One of the unforeseen problems that we encountered was our use of a phase *delay* as the shift. As has been shown several times at these meetings, acclima-

tion after a phase delay occurs more rapidly than following a phase advance. In projecting further studies of this nature, I think that phase-shift advance would be a better test of a possible chronobiotic than a phase delay.

Our conclusions were that Quiadon<sup>®</sup> did not make that much difference between the physiological adjustments of the control and the drug groups. As Dr. Weitzman has commented, after phase-shift, there are difficulties sleeping. This compound's action as a tranquilizer in allaying anxiety did promote better sleep. The one complicating factor was that Quiadon<sup>®</sup> also acted as a mild diuretic so, at least on several occasions, sleep was abruptly interrupted by an urge to evacuate the bladder.

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## HEALTH AND WORK SHIFTS: DISCUSSION II

*Jadwiga Wojtczak-Jaroszowa*

Recognition of the criteria helpful for evaluation of day-night variations in physical fitness, as well as mental performance of human beings, seems to be of great importance for practical reasons.

Our investigations in this field, made with A. Banaszekiewicz and E. Sprusinska, consisted in comparison of subjective and objective responses to prolonged intermittent physical exercise performed at different times of the day. The examined subjects (20 students) were pedaling on an ergometer at a constant external work of about 30% of the individual's  $V_{O_{2max}}$  for eight hours: between 8 a.m. and 4 p.m. (Morning-Afternoon Session), 4 p.m. and Midnight (Afternoon-Evening Session), and between midnight and 8 a.m. (Night-Early Morning Session). During the work, the pulse rate and oxygen uptake were measured (as the objective symptoms) and, at the same time, subjective responses via interviews to physical load were collected.

It was shown that, in all sessions, oxygen consumption, Figure 1, was lowest during the first hour of the work and increased after four and eight hours of cycling. Most visible increment was noticed for Afternoon-Evening Session during which the oxygen consumption (in absolute values) reached the highest level at midnight. Similar direction of changes was observed for each session in relation to pulse rate, Figure 2, as well as, to subjective symptoms, Figures 3a, 3b, 3c, 3d.

To assess the variation in relation to the different time of the day, the results were collected separately for 30 minutes, four hours and eight hours of riding. It was noted that the rate of objective, as well as subjective responses to short-lasting (30 minute) cycling, was similar for three different times of the day: 8:30 a.m., 4:30 p.m. and 12:30 a.m.

During the prolonged work, some significant divergence between subjective and objective responses was observed for work lasting eight hours, Figure 4. Namely, the oxygen consumption reached the highest level at midnight (Afternoon-Evening Session) and the pulse rate was lowest at the same time. On the contrary, the subjective responses were most extensive for Night-Early Morning Session, at 8 a.m. The conclusion is that when the results obtained for different times of the day are

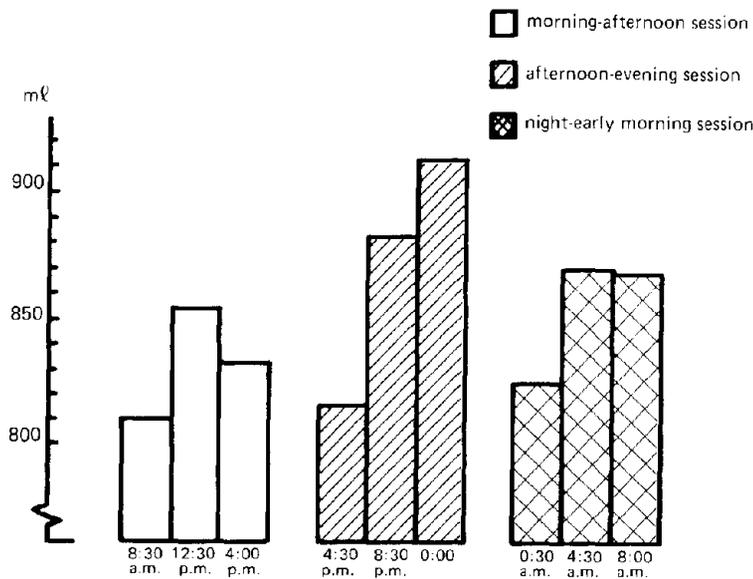


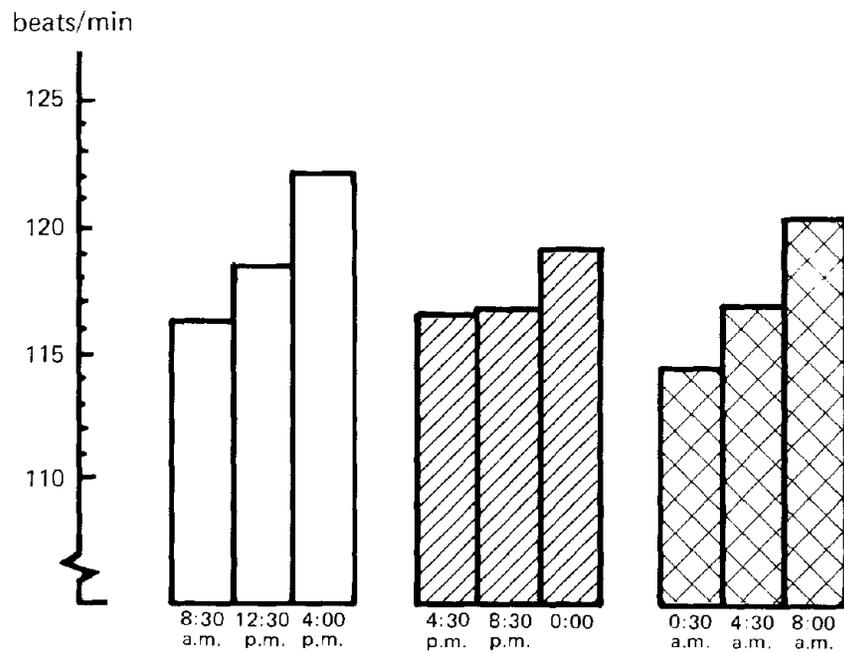
Figure 1. Oxygen consumption during prolonged work at different times of day (women).

compared, so-called objective responses to physical work do not correlate with actual self-rating of the fatigue.

In the second part of our experiments (performed with Z. Makowska), the influence of physical work on sensory-motor performance was studied at different times of the day. This investigation was carried out among 20 men and 23 women students who performed different kinds of psychomotor tests during each session. Two types of experiments were performed: during experiment I, the subjects rested between successive tests; in Experiment II, they were physically active between cycling periods on the ergometer. More or less extensive day-night variations indicated a worsening of performance in early morning hours. It is interesting that the amplitude of these variations was higher when the subjects were physically active between the successive tests, (Experiment II, Figures 5a, 5b, 6a, 6b, 7a, 7b, 8a, 8b). A lowering of the men's performance at night was especially marked.

Results of experiments indicated that the following conclusions can be drawn:

- (1) There was no discordance in subjective and objective (in absolute values) responses to short moderate work performed at different times of the day.



*Figure 2. Pulse rate during prolonged work at different times of day (women).*

- (2) Some divergence between these responses was observed when the work was done for many hours. There was a higher rate of subjective feeling of fatigue at night (or after night work) while the objective responses (pulse rate measured in absolute values) were lowest at night.
- (3) Nightly dip of sensory-motor performance of human beings was more extensive when physical work was performed between cycling periods.

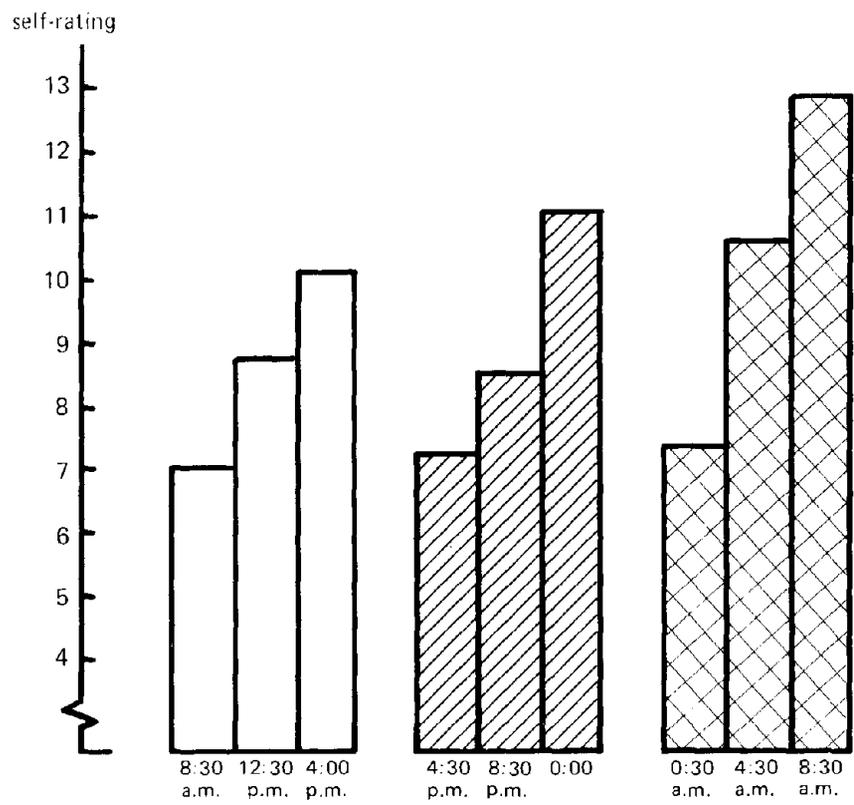


Figure 3a. General feeling of fatigue (worn out, working hard, physically tired, listless) during prolonged work at different times of day (women).

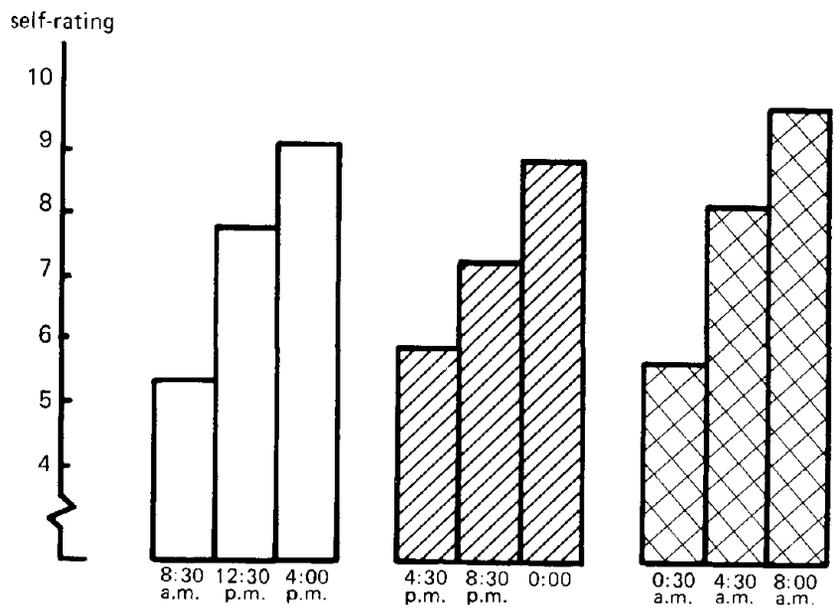


Figure 3b. Muscular fatigue (weak legs, physically tired, aching muscles of legs, muscle tremors) during prolonged work at different times of day (women).

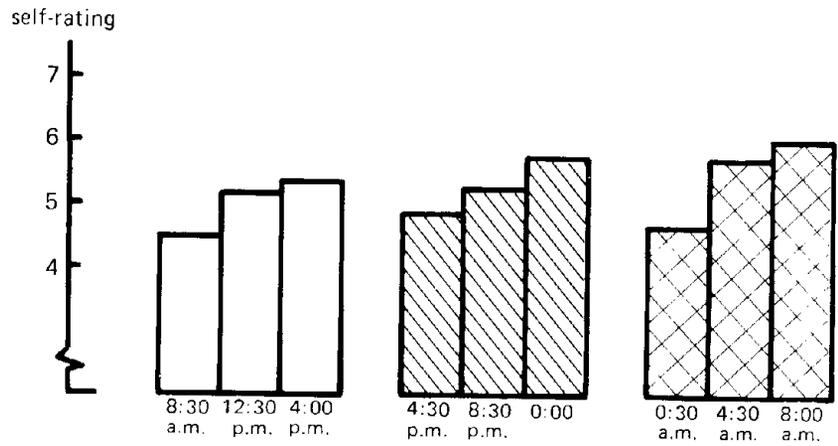


Figure 3c. Somatic symptoms (hard to breathe, short of breath, heart pounding, panting) during prolonged work at different times of day (women).

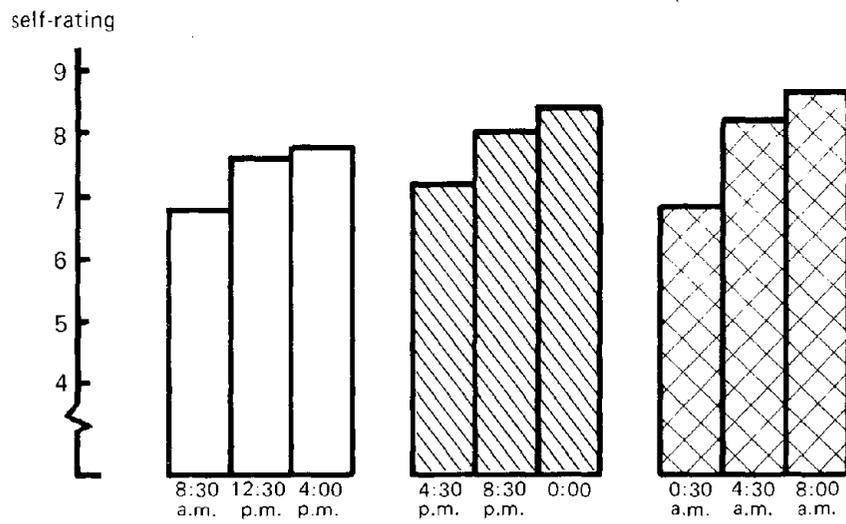


Figure 3d. Symptoms connected with thermoregulation (dry mouth, sweating, thirsty, overheating) during prolonged work at different times of day (women).

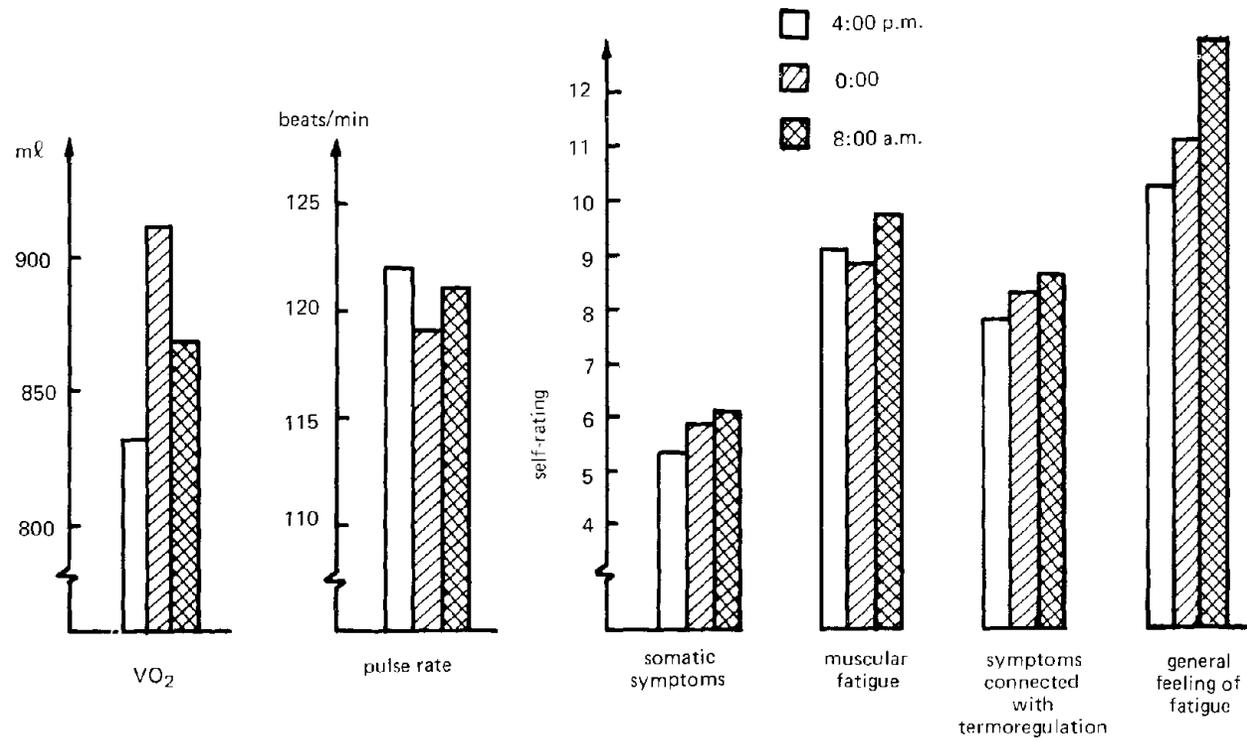


Figure 4. Objective and subjective responses to 8-hours intermittent work at different times of day (women).

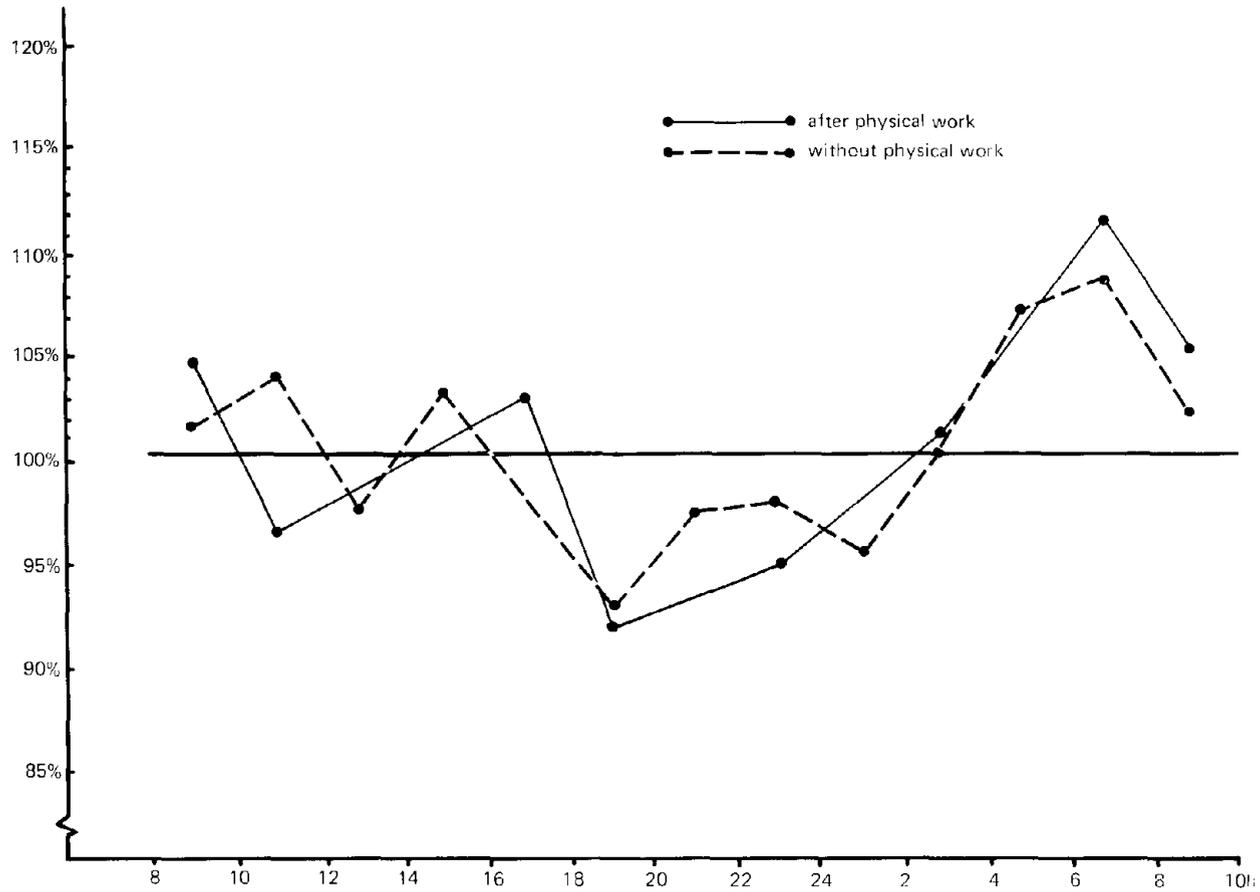


Figure 5a. Visual reaction time (men).

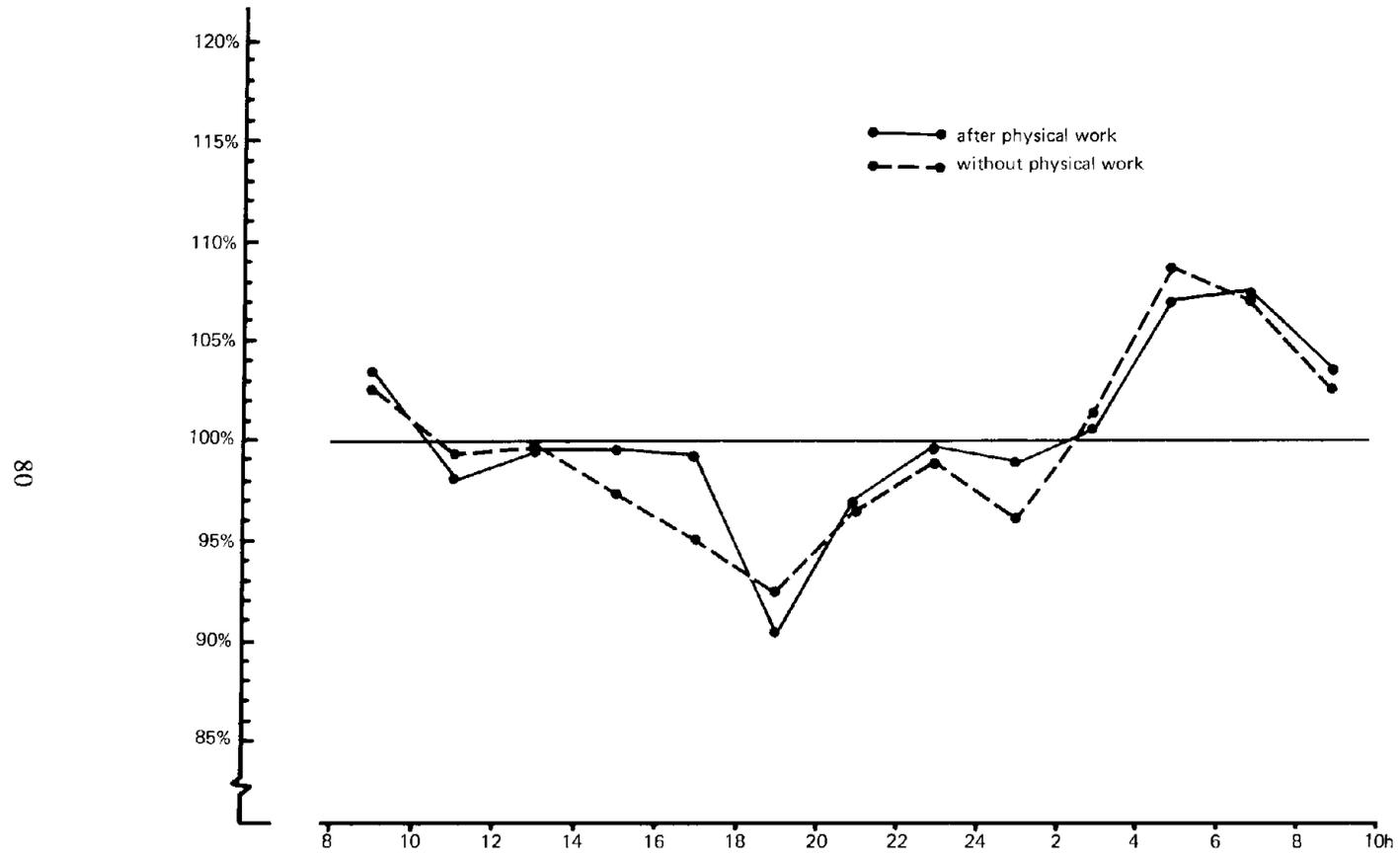


Figure 5b. Visual reaction time (women).

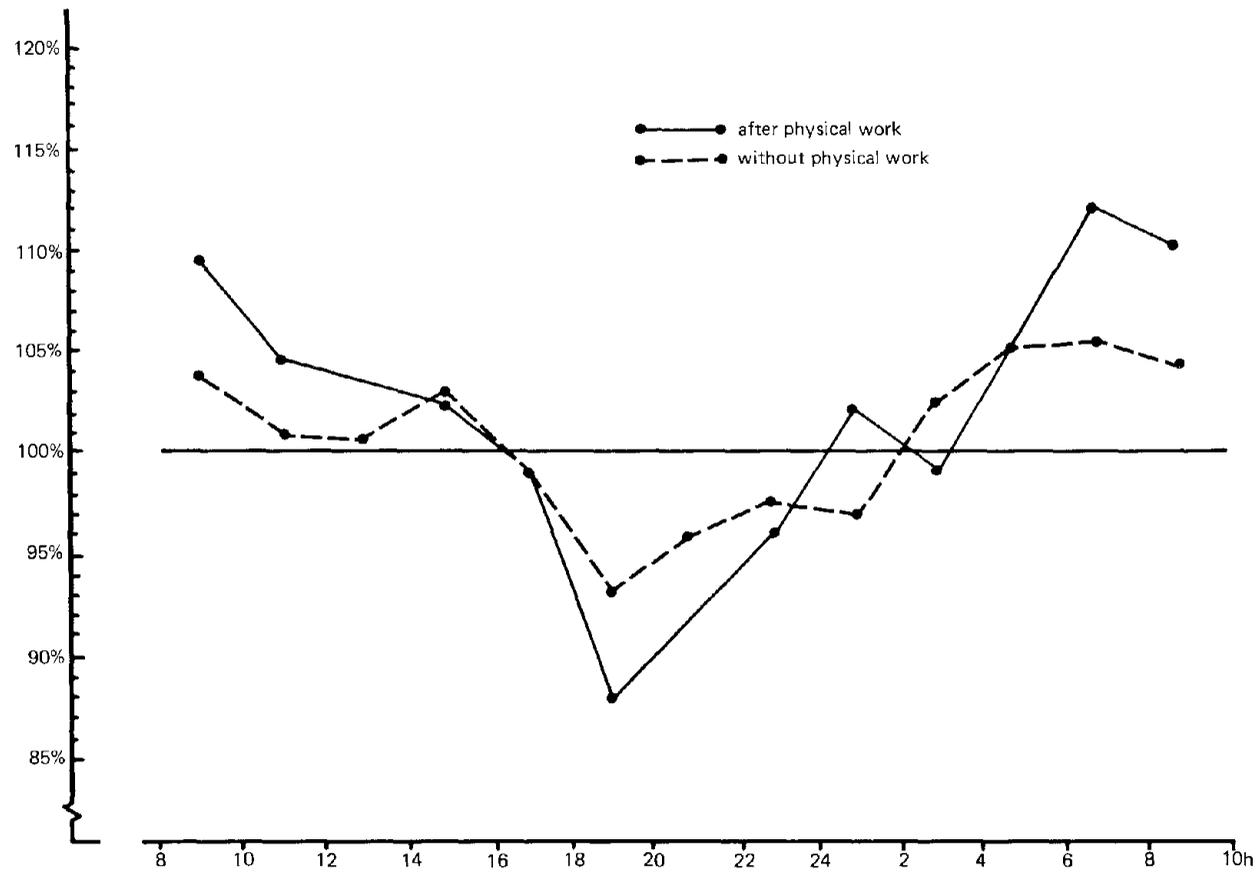


Figure 6a. Auditory reaction time (men).

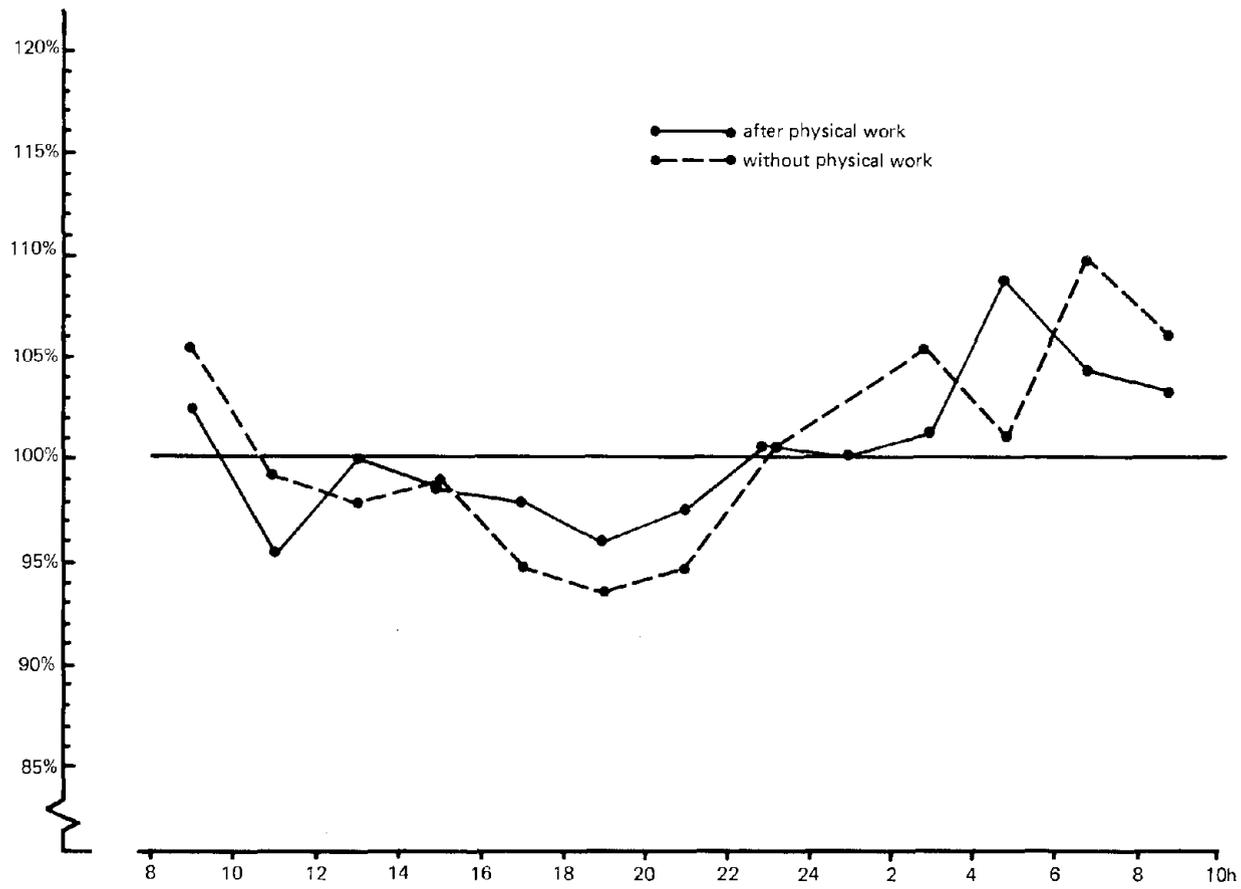


Figure 6b. Auditory reaction time (women).

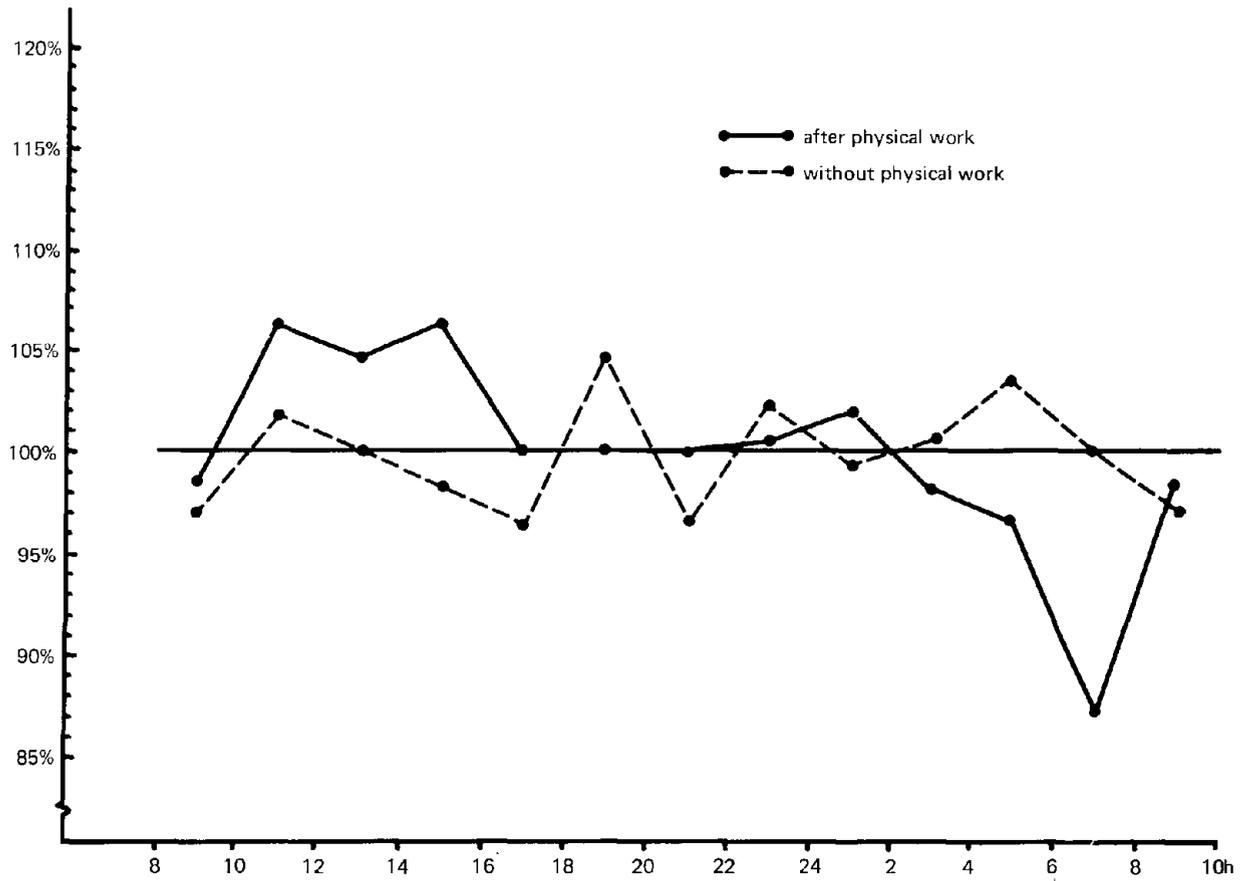


Figure 7a. Learning test (men).

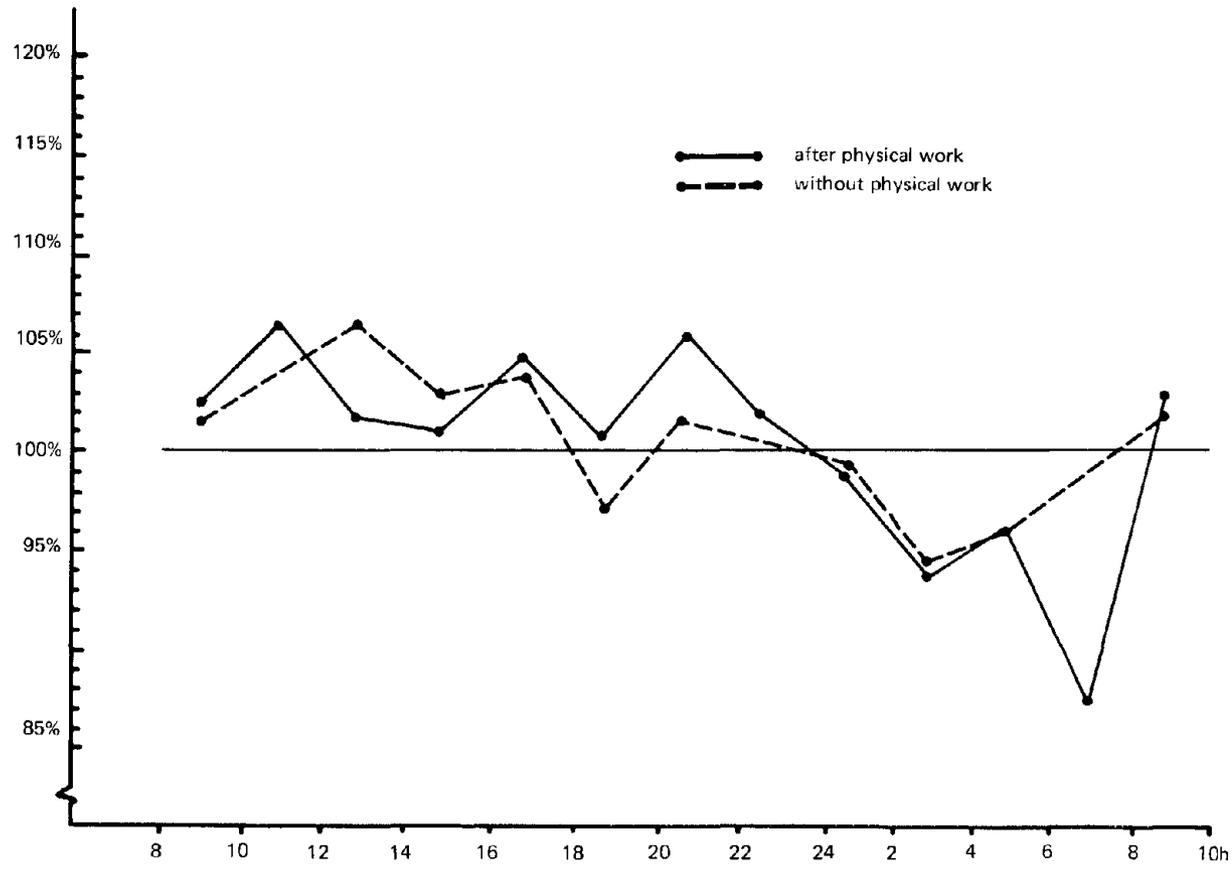


Figure 7b. Learning test (women).

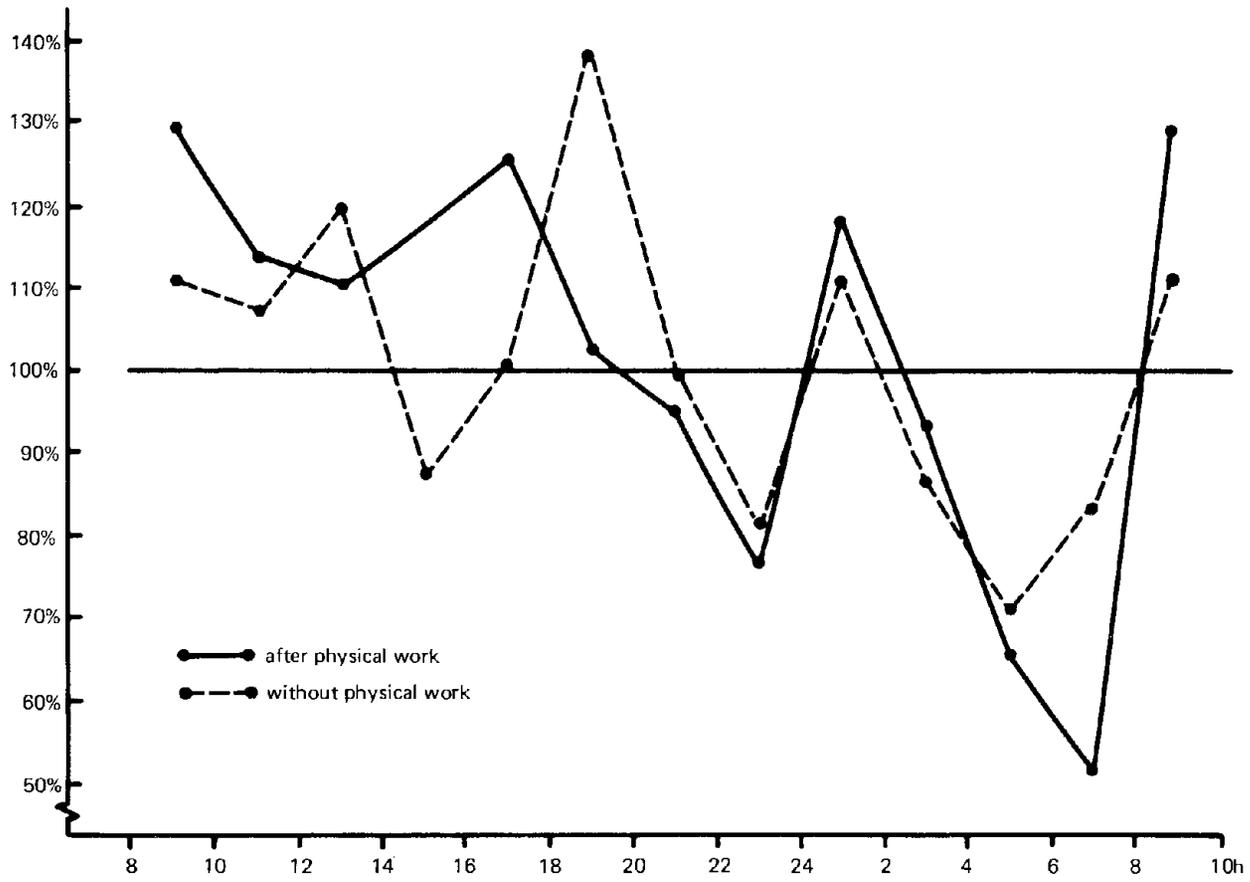


Figure 8a. Recalling test (men).

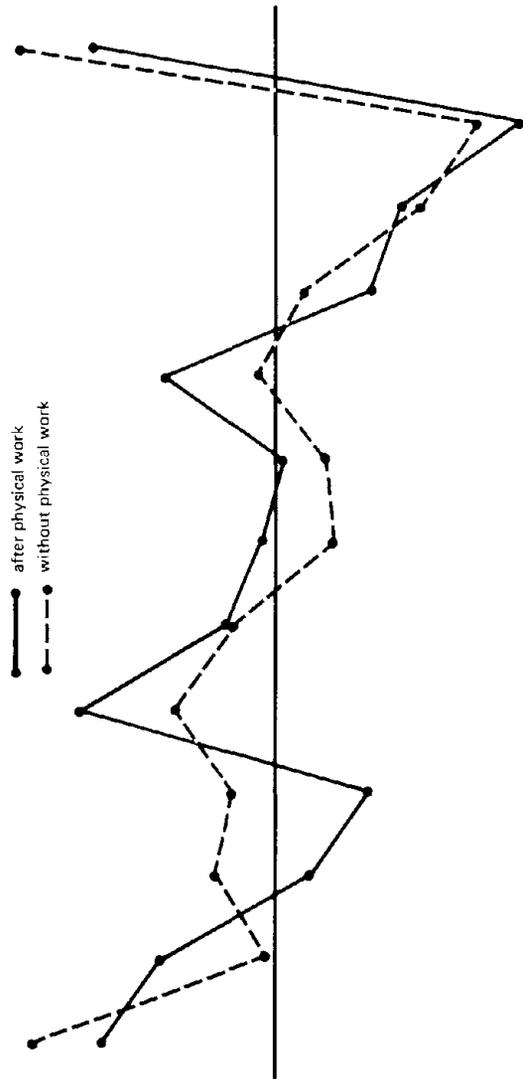


Figure 8b. Recalling test (women).

# PHARMACOLOGICAL AND TOXICOLOGICAL CORRELATES OF CIRCADIAN SYNCHRONIZATION AND DESYNCHRONIZATION

*Erhard Haus*

Biologic rhythms in the circadian frequency range are found almost ubiquitously in metabolizing structures at the subcellular, cellular and higher levels of biologic organization. Synchronization of circadian periodic cell functions within an organ leads to an orderly sequence of physiologic events which are characteristic for normal organ function. Circadian rhythms of metabolic functions usually show certain and, under standardized conditions, reproducible phase relations among each other. The acrophases of the functional metabolic processes e.g. the secretion of an endocrine gland and the glycogen production and storage in the liver usually are found to show a phase difference from the acrophases of the rhythms of cell reproductive functions i.e. parenchymal cell multiplication, Figure 1. The circadian rhythms of a given organ are synchronized with those of other organs and with the organism as a whole by neural, endocrine and possibly other circadian periodic metabolic functions. These in turn are synchronized with the astronomic day-night cycle by environmental factors like sleep-wakefulness, light-dark cycle, social routine or food uptake.

The hypothalamus, pituitary and adrenal cortex are a pertinent example of the interaction of cellular and organismic rhythms with rhythms of several superimposed controls which together form a complex and in several frequency ranges periodic endocrine system. Figures 2 and 3 summarize extensive *in vivo* and *in vitro* work of this laboratory defining the interaction of hypothalamic pituitary and adrenal factors which characterize the circadian adrenal cycle in the Balb/c mouse. After the injection of an identical amount of saline or ACTH, the response of serum corticosterone varies as a function of the stage of the adrenal cycle at the time of injection. The greatest response to the saline injection occurred four to eight hours prior to the circadian corticosterone peak.

The reaction of the Balb/c mouse adrenal to exogenous ACTH, however, is maximal four to eight hours thereafter and is lowest at the

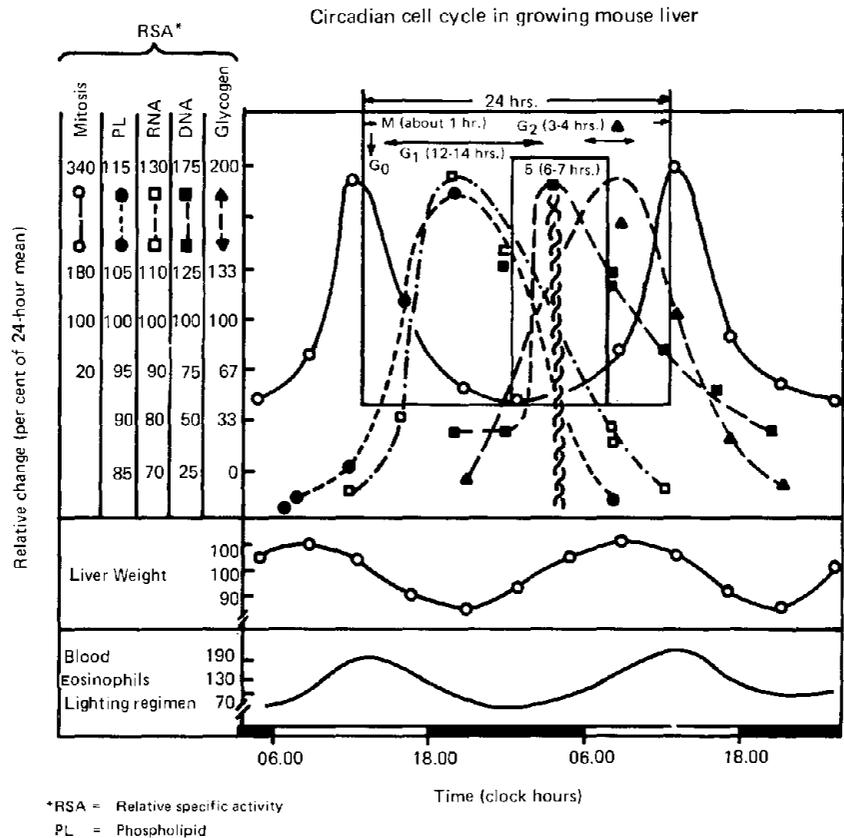


Figure 1. Circadian rhythm in cell metabolism and cell division in growing mouse liver. Phase relationship of different cellular processes:  $^{32}\text{P}$  labelling of phospholipid (PL), RNA and DNA; glycogen content, mitosis and liver weight in relation to a regimen of alternating light and darkness. RSA, relative specific activity.

The relative frequency with which certain stages of the cell cycle will occur at certain times is predictable under standardized experimental conditions. Similar circadian and other rhythmicity — with definable phase relations — characterizes many mammalian tissues.

crest time of serum corticosterone concentration, i.e., the time of the physiologic peak in adrenal function. This is apparent in the difference between the saline injected and the ACTH treated animals, which represents the exogenous ACTH effect proper. The serum corticosterone

|            |          |       |      |      |      |      |      |
|------------|----------|-------|------|------|------|------|------|
|            | Controls | 54/10 | 27/5 | 34/6 | 27/5 | 27/5 | 34/6 |
| No of      | Saline   | 54/10 | 26/5 | 33/6 | 27/5 | 27/5 | 33/6 |
| Mice/Pools | ACTH     | 55/10 | 27/5 | 34/6 | 26/5 | 27/5 | 34/6 |

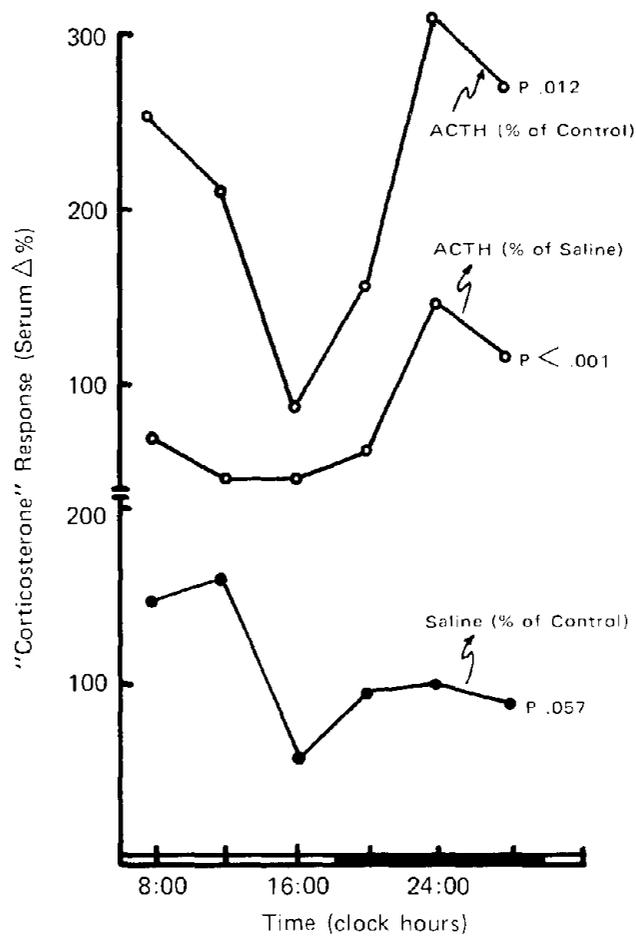


Figure 2. Percent change in serum corticosterone concentration after the injection of saline and ACTH in different stages of the adrenal cycle.

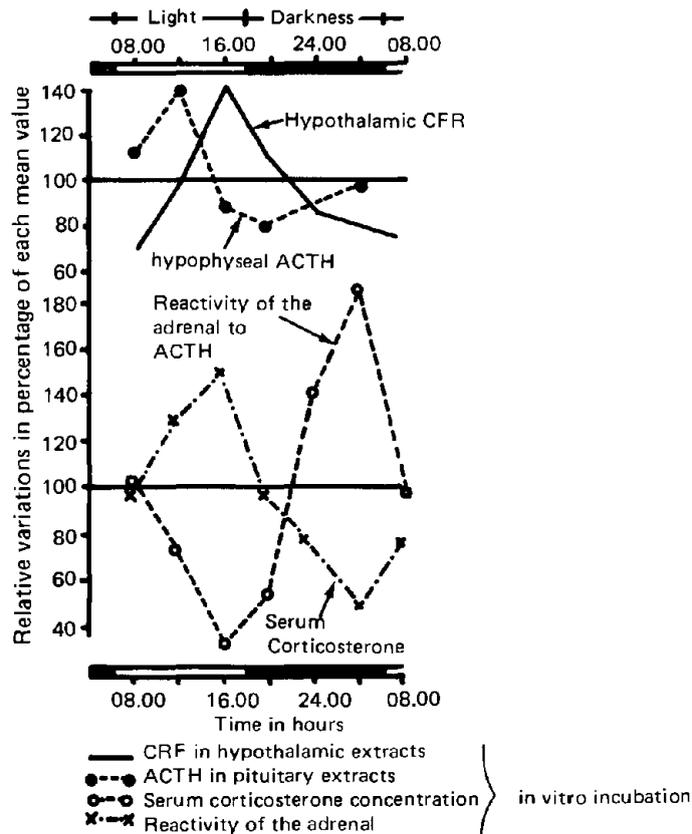


Figure 3. The time relationship of several hypothalamic-pituitary- adrenal rhythms in the male C-mouse, as established by *in vitro* studies (Ungar and Halberg<sup>90</sup>), may determine the response of the intact animal to saline injection and to exogenous ACTH, Figures 1 and 2.

response in the Balb/c mouse after saline injection and ACTH constitutes a periodic function dependent upon the stage of the adrenal cycle in which the stimulus is applied. The same initial values in different stages will lead to different corticosterone values after stimulation. These *in vivo* results were extended by *in vitro* studies by Ungar and Halberg, the results of which are summarized in Figure 3. The mouse adrenal removed at different circadian system stages as indicated by the synchronizer schedule (lighting regimen) at the bottom of Figure 3, showed also *in vitro* a circadian periodic response to ACTH.

Confirming the results obtained in the intact animal, Figure 2, the maximal response of the mouse adrenal to ACTH *in vitro* occurs during the middle and second half of the daily dark span. The minimal response occurs at the end of the light span and at the beginning of the dark span when the adrenal is at the peak of its circadian activity cycle as expressed by the peak of serum corticosterone concentration.

Pituitary ACTH content and hypothalamic corticotropin releasing factor (CRF) content were determined by bioassay. The pituitary ACTH content also showed a circadian rhythm. The acrophase of this rhythm and the macroscopically highest ACTH content in the gland precede by four to eight hours the physiologic peak in serum corticosterone values. The CRF activity in the hypothalamus on the other hand is found to be highest at the time of the highest serum corticosterone levels which indicate the circadian peak of adrenal activity, Figure 3. The *in vitro* results confirm and extend the findings obtained in the intact animals. The buildup and storage of ACTH in the pituitary precede the daily peak of adrenal function and thus may account for the increased response to saline injection of the intact animals during this circadian system stage. The corticotropin releasing activity in the hypothalamus is low at the time when the ACTH content in the pituitary is increasing and at its peak. It rises and reaches its highest values at a time when the pituitary ACTH content is decreasing rapidly and when it reaches its lowest levels during the 24-hour span. It has to be kept in mind, of course, that the hormone content of an endocrine organ does not necessarily reflect the activity at a given time although this has been claimed for example for the adrenal cortex in the rat.

The findings in the Balb/c mouse suggest that the stage of metabolism in the adrenal cortex and the stage of various superimposed controls determine changes in the gland's reactivity along the 24-hour scale which are significant in extent and can predictably be dissociated in timing. The time four to eight hours prior to the physiologic maximum in adrenal cortical function seems to be characterized by an optimal preparedness of the pituitary, and possibly its superimposed controls, to release an increased amount of ACTH either spontaneously at the right circadian system stage or prematurely in response to environmental stimuli. The adrenal cortex, on the other hand, becomes maximally responsive to ACTH and remains so after the stage of its physiologic activation at a time when only little endogenous ACTH seems to be available.

The finding that the ACTH response in nocturnal rodents is greater at about midnight provides the experimental background for observations of Perkoff et al, Forsham et al, Nugent et al and Martin and Hellman who had found a greater response of human adrenal to exogenous ACTH during the daytime for a limited number of cases in diurnally active men.

The difference in timing between the pertinent rhythms of the two species is about 12 hours, as had been demonstrated previously for the cycle in blood eosinophils and serum corticoids, among other functions.

Circadian rhythmicity, as such, is independent of outside time cues and, if once established, persists in many experimental models *in vitro* and *in vivo* under, as far as feasible, constant environmental conditions. Under such circumstances, however, a circadian system may show frequencies slightly but consistently different from 24 hours and thus become free-running from the astronomic day-night cycle. Non-24-hour free running circadian systems have been found and studied in the rodent after elimination of the dominant synchronizer, the light-dark change, e.g., under conditions of constant light or constant darkness. Free-running is equally observed after interference with light perception, e.g., by optic enucleation. In the free running state, the phase relations between different physiologic rhythms either may remain unchanged, Figure 4, or internal desynchronization may occur.

In the case of a phase-shift of one or of several external synchronizers, circadian periodic body functions may change their acrophase accordingly. They will do so whenever the dominant synchronizer of a given function is shifted, for different synchronizers may be dominant. For example, the circadian rhythms serum iron and serum insulin are susceptible to phase-shift by a change in diet habits, Figures 5,6, while the circadian rhythm of plasma cortisol under the same experimental conditions is not, Figure 7. The phase-shift of a circadian periodic function, however, does not occur abruptly but gradually through a number of transient cycles. Alternatively a phase-shift may be brought about by the appearance of a new peak and obliteration of the previous one until a new "phase-shifted" acrophase becomes demonstrable. The time required for a phase-shift appears to be characteristic for each body function. Figures 8a and 8b show the phase-shift of three concomitantly studied circadian periodic parameters in BALB/c mice after a 12-hour shift in lighting regimen. Figure 9 shows the phase adaptation of several human body functions after two intercontinental flights over 6 resp. 7 time zones. Some functions, like sleep-wakefulness and body temperature, seem to phase-shift quite rapidly while others, like the circadian rhythms in adrenocortical function, liver glycogen content in the mouse and electrolyte excretion in man, show a slower phase adaptation, Figures 8 and 9.

In the mouse, a 180°-phase shift in body temperature usually is achieved within six to seven days. A comparable shift in liver glycogen, however, is observed under identical conditions only after about nine days and the circadian cycle in pinna mitoses was found to be inverted only after two to three weeks.

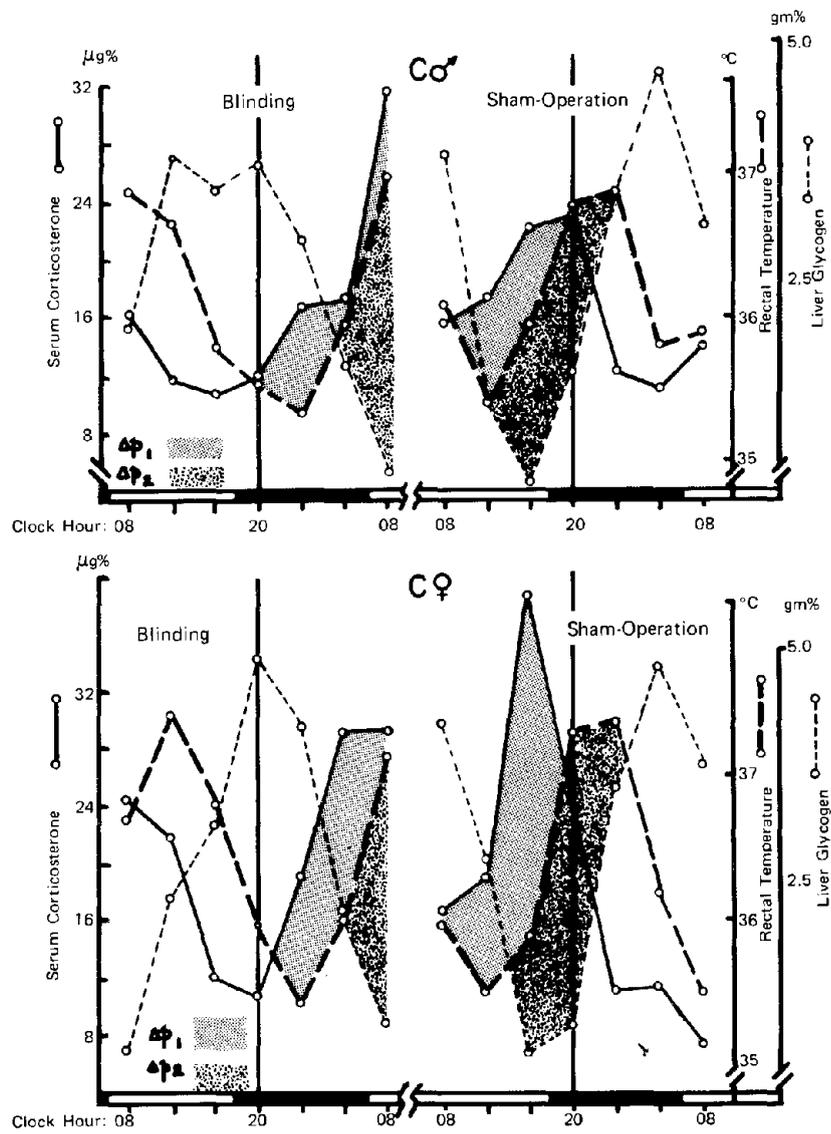


Figure 4. Time relations of circadian rhythms in liver glycogen, serum corticosterone and rectal temperature in *C* mice at 21 days after surgery.

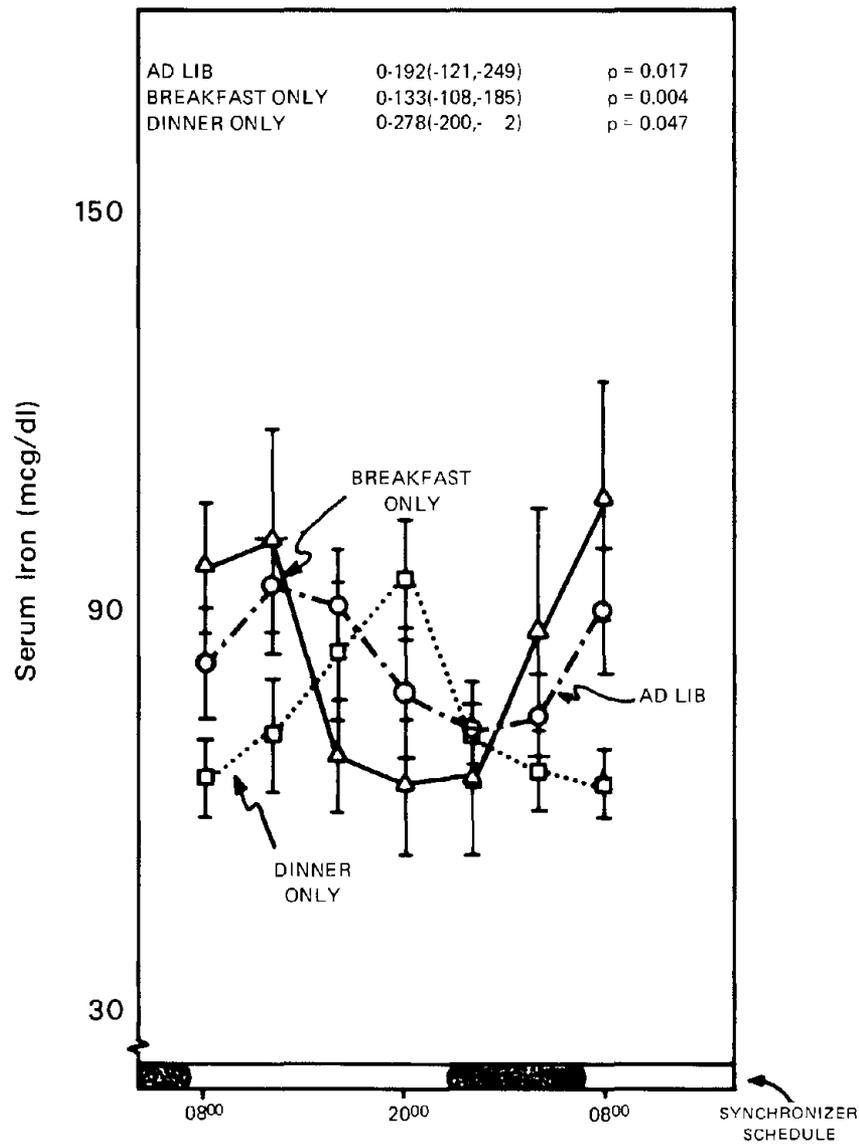


Figure 5. Phase-shift of circadian rhythm in serum iron by meal-timing.

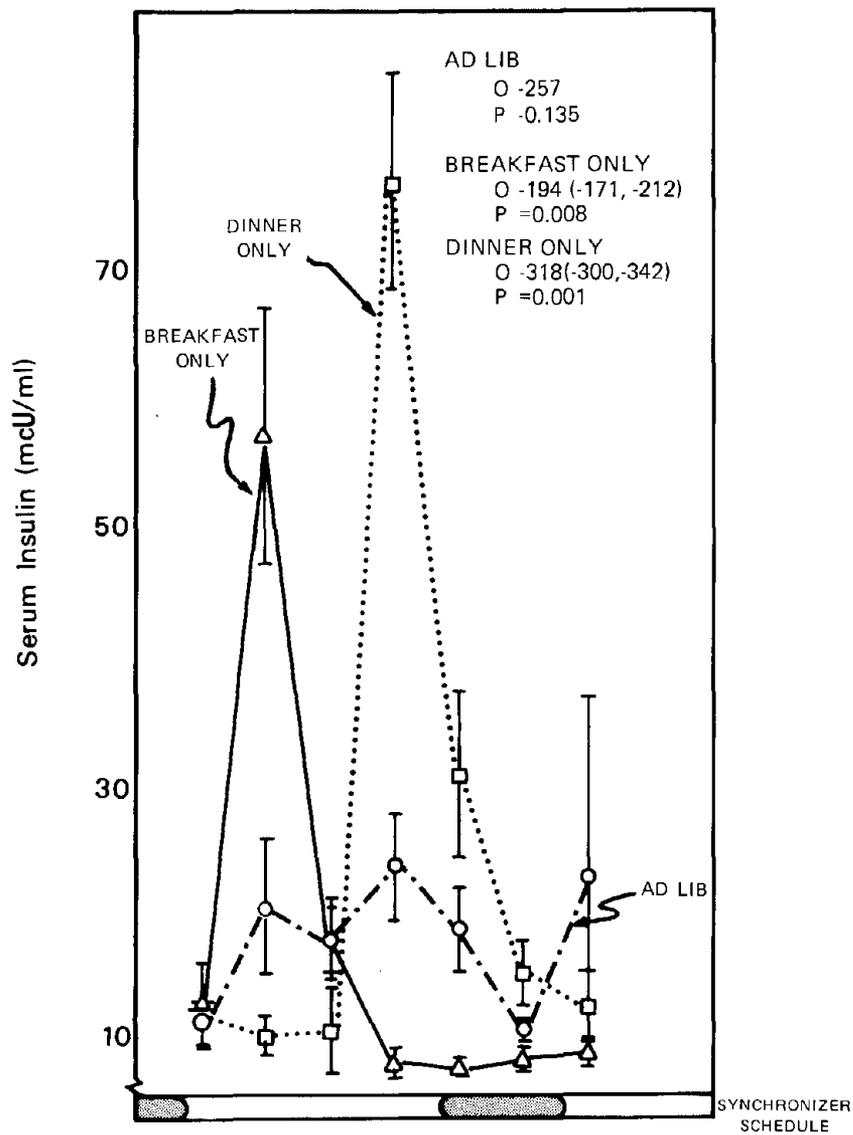


Figure 6. Phase-shift of circadian rhythm in serum insulin by meal-timing.

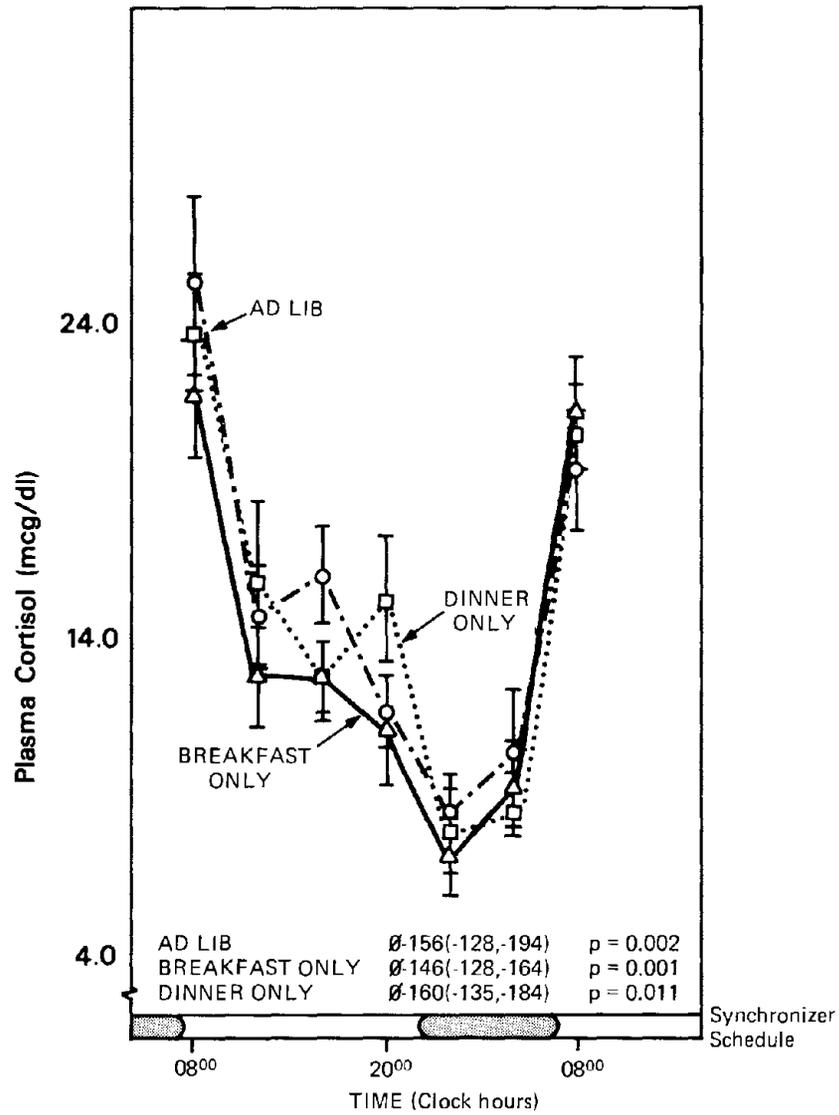


Figure 7. Plasma cortisol rhythm unchanged by meal-timing.

Chronograms on Circadian Rhythm of Serum Corticosterone and Rectal Temperature in 828 Male C Mice Subjected to a Change in Phase of Synchronizer ( $\Delta\phi_s$ ) and in Controls

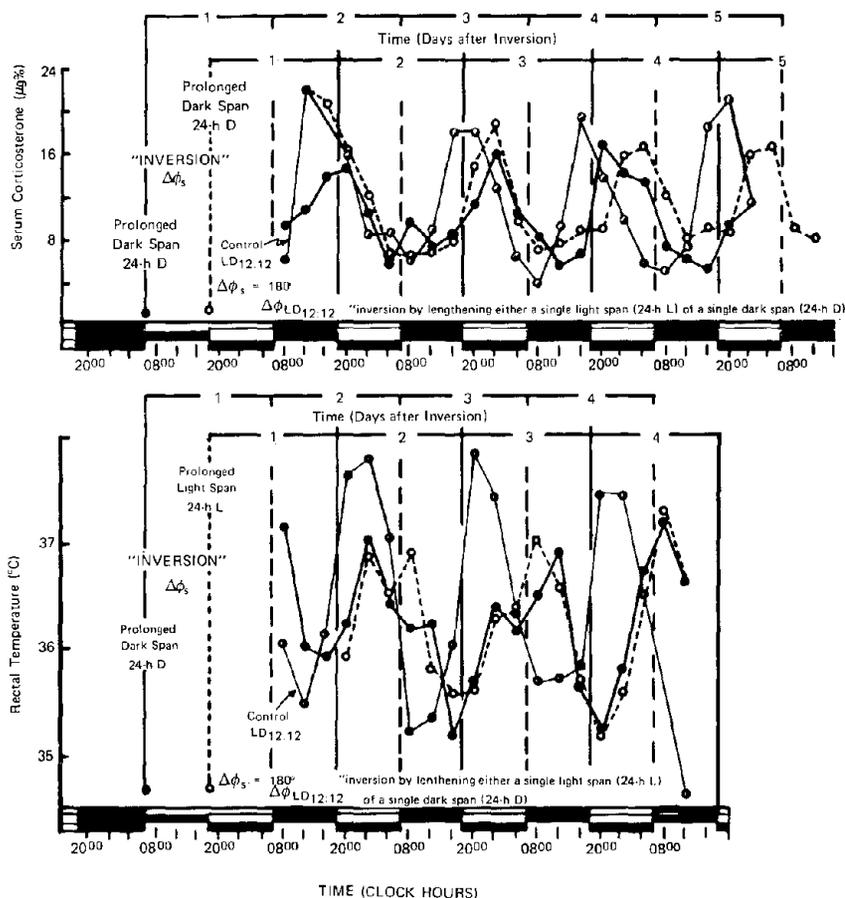


Figure 8a. Occurrence, in 1963 study, of a circadian phase-shift macroscopically displayed for serum corticosterone and rectal temperature; such chronograms of external timing do not suffice for a quantification of the shift characteristics.

During an ongoing phase-shift the organism appears to be in a state of internal desynchronization with alteration of the usual phase relations between circadian periodic functions. The question arises whether such alterations may be detrimental to the organism function and to its ability to withstand noxious stimuli. Thus far, very little information on these aspects of phase alterations has become available. It appears that an impairment of the resistance to noxious stimuli under conditions of synchro-

GRADUALLY SHIFTING CIRCADIAN ACROPHASE  
 OF RECTAL TEMPERATURE, SERUM CORTICOSTERONE AND LIVER GLYCOGEN  
 During Days 2-5 Following a 180° Shift in Lighting Regimen (828 ♂ Mice)

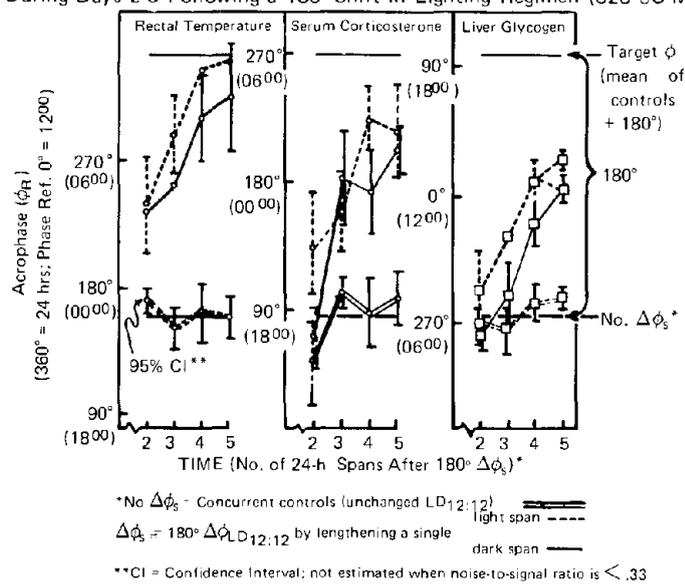


Figure 8b. Microscopic summary of phase-shifts displayed in Figure 8a and of corresponding data for liver glycogen rhythm from the same 1963 study. Shift rate of liver glycogen rhythm differs from that of rectal temperature.

nizer alteration may be found for some but not for other (e.g. Ouabain) agents.

The circadian periodic changes in cell and organ functions lead in the circadian synchronized individual to predictable changes in sensitivity and/or resistance to a multitude of physical, chemical, hormonal and other agents. By an experimental design in which the stimulus to be applied at different circadian system phases is kept constant while the physiologic state of the organism is allowed to vary, as it does whether or not one wishes to evaluate such variations statistically, highly significant susceptibility-resistance cycles of experimental animals and recently also of human subjects have been demonstrated. Thus circadian cycles of responsiveness characterize agents such as noise, which acts within seconds to induce audiogenic convulsions in susceptibility of rodents to injury from agents which act within minutes, such as acetylcholine, pentobarbital and Ouabain; or within hours such as ethanol and SU 4885 (Figure

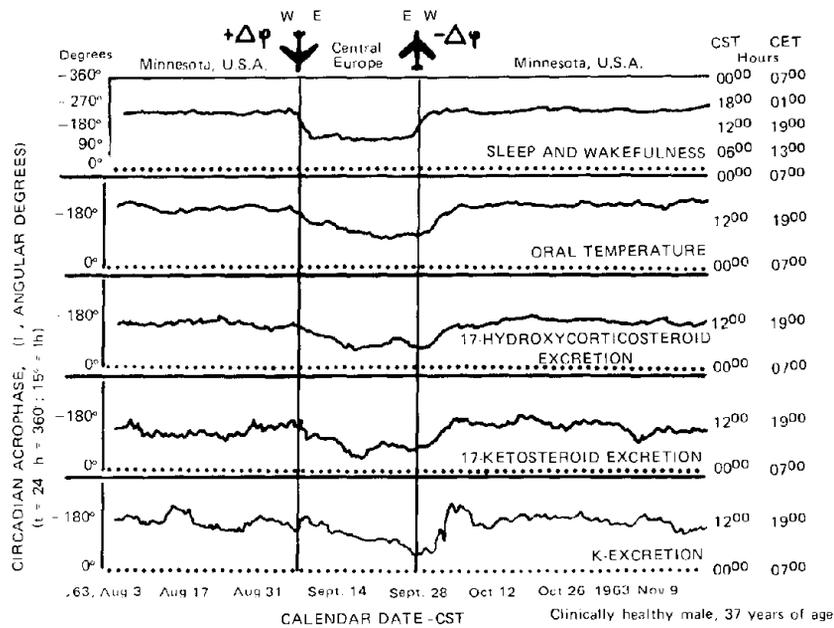


Figure 9. Temporal phase diagram showing phase adaptation of five circadian periodic functions after rapid change in synchronizer schedule. The two phase-shifts of the circadian system shown occurred following intercontinental flights (Minnesota, U.S.A. to Central Europe for 22 day and return to Minnesota).

10). The effect of bacterial endotoxins which act within days, and even of certain chemical carcinogens, which manifest their effects only after several months, also depends predictably upon the circadian system stage of the arrival at the moment when a given agent is administered.

From a large amount of information accumulated during the last two decades on circadian periodic changes in responsiveness, sensitivity and resistance *in vivo* as well as *in vitro*, it can be concluded that in a periodic system a stimulus applied at different stages will elicit a quantitatively and in some instances qualitatively different response, Figure 11. In the case of a potentially toxic drug, the drug's effect, if given at one stage of the subject's rhythmic system, may jeopardize the well-being of the organism even to the point of death, while the identical dose of the identical compound given at another stage may be inadequate to even achieve the therapeutically desirable result, Figure 11, top. Thus, in order to achieve a satisfactory therapeutic effect, and to avoid jeopardy to the subject to

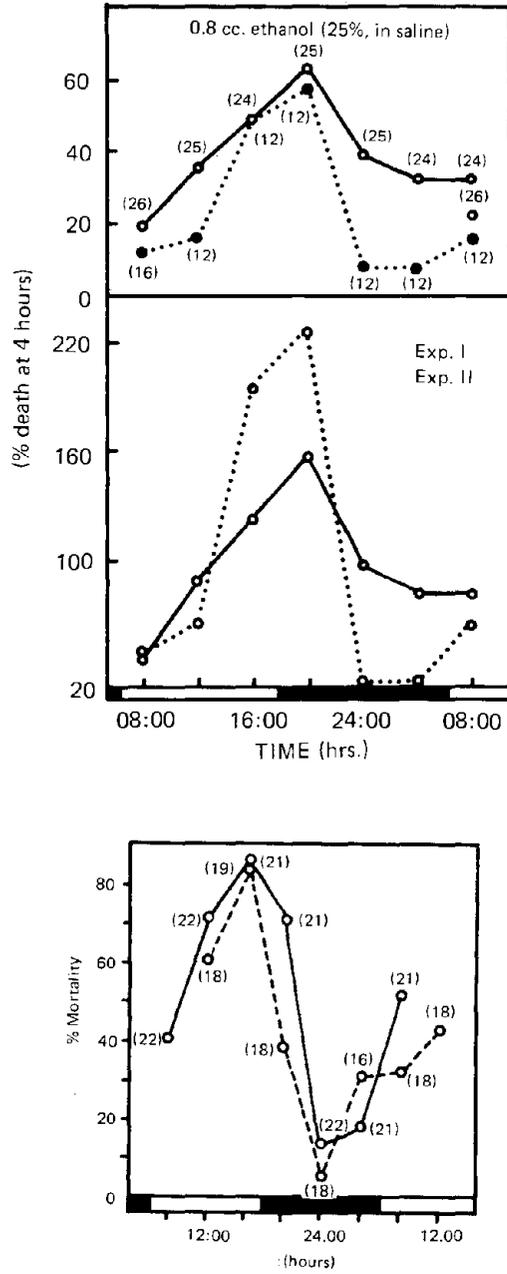
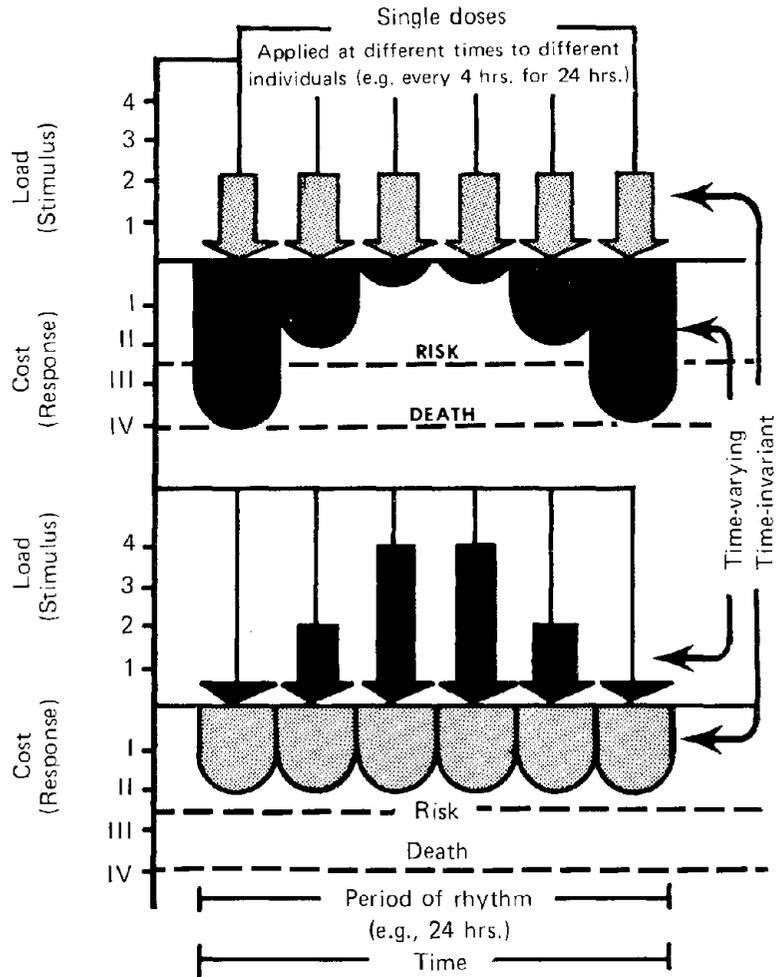


Figure 10. Circadian susceptibility-resistance cycle to ethanol in male *C* mice. Two separate experiments. Deaths as percentage of total tested (in parentheses) shown on top. Same data are converted below into percentage of overall mortality.

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 11. Hours of changing responsiveness or resistance and their chronotherapeutic implications. In a periodic system, the identical stimulus given at a different system stage will elicit a sometimes drastically different response (top).

In the case of, e.g., a toxic drug this response may, at the low point of an organism's susceptibility cycle, lead to damage or even to death of the subject, while at another time the same dose may be inadequate even to reach its desired effect. Chronotherapy with adjustment of the dose according to the stage of the susceptibility rhythm (bottom) may reach the desired effect without even incurring a risk for the subject.

be treated, the dose of the drug has to be adjusted according to the state of the subject's sensitivity cycle, Figure 11, bottom. In order to achieve this goal, the sensitivity-resistance cycle toward this specific agent has to be known and has to be mapped by previous investigation. Since the mechanisms involved in the circadian periodic changes in responsiveness and sensitivity do vary with the specific action of a given agent the timing of its sensitivity cycle is characteristic for each agent. Differently acting stimuli thus have to be expected to show differences in the acrophases of their susceptibility resistance cycle, Figure 12.

If an organism is experiencing a phase-shift of its circadian system or of certain components of its circadian system which follow one or the other dominant synchronizer (e.g., time of food uptake, lighting regimen, etc.) a phase-shift of the circadian cycles in responsiveness, sensitivity and resistance has to be expected. Each of these cycles presumably will follow the phase-shift of the circadian rhythms of those body functions which critically determine the organism's response to the specific agent. Significant differences in shift-time of different susceptibility-resistance cycles thus have to be expected.

The amenability of susceptibility-resistance cycles in experimental animals to phase-shifts induced by a change in lighting regimen has been documented for numerous agents, e.g., for toxic doses of ethanol, Figure 13, whole body x-radiation, Figures 14, and 15, etc. More recently, phase-shifts of drug susceptibility have been achieved by limitation of food uptake of animals to certain circadian system stages.

Phase-shifting of circadian periodic functions and of the related susceptibility-resistance cycles to certain agents by one or the other environmental synchronizer may in the future serve as a tool for the exploration of mechanisms of pharmacologic actions and of drug effects on complex biologic systems similar to the use of chromatography in analytical chemistry. Although an identical time shift of a circadian periodic function (e.g., the mitotic rate in bone marrow) and of a sensitivity-resistance cycle (e.g. to whole body x-radiation) does not imply a causal relation between the two, a different shift time or differences in the response to certain synchronizers (e.g. lighting regimen or diet) would almost certainly exclude a critical connection between these functions.

An area of considerable current interest in chronopharmacology is the application of chronopharmacologic concepts to the chemotherapy and radiotherapy of cancer. In the treatment of human malignancies, agents have to be used which are inherently toxic to both host and tumor and the therapeutic effect is based on the observation, or hope, that the tumor will be more damaged by a given treatment than the host. The extension

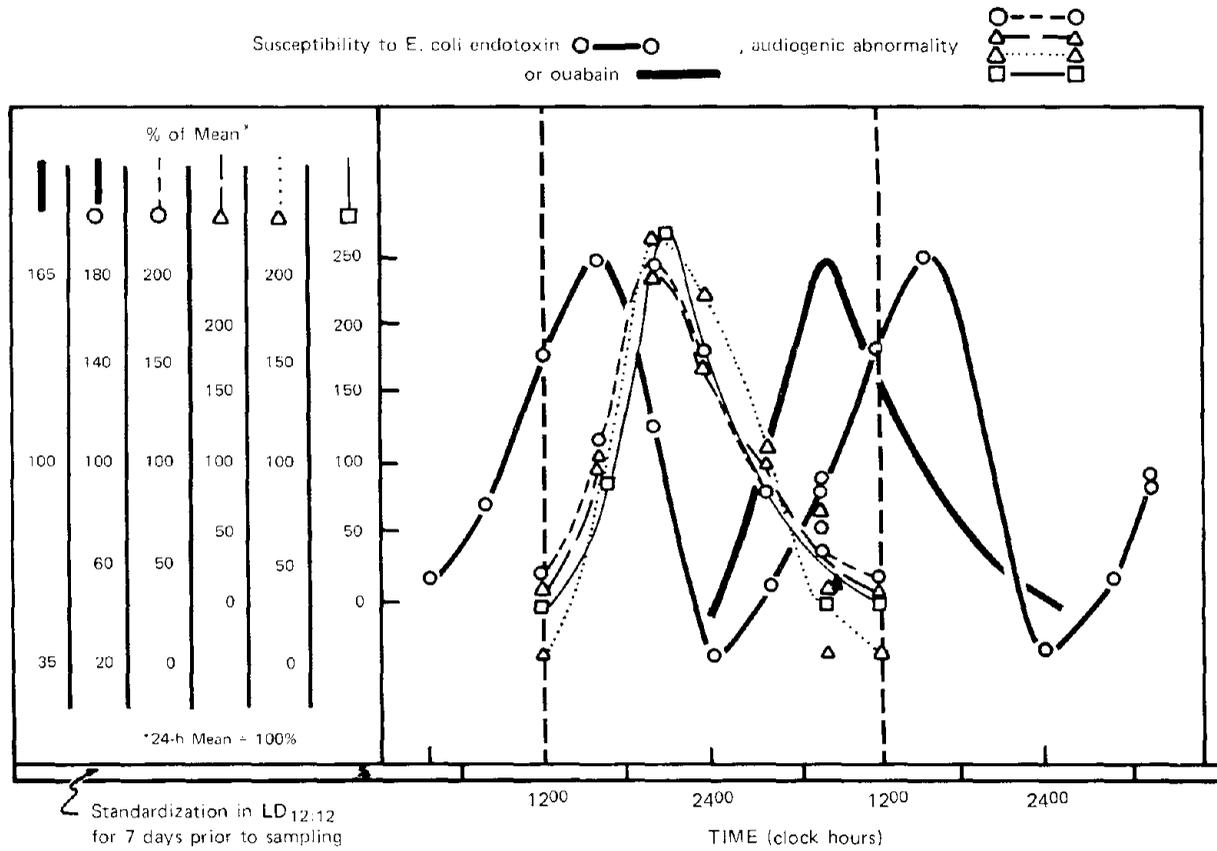


Figure 12. Hours of Changing Resistance.

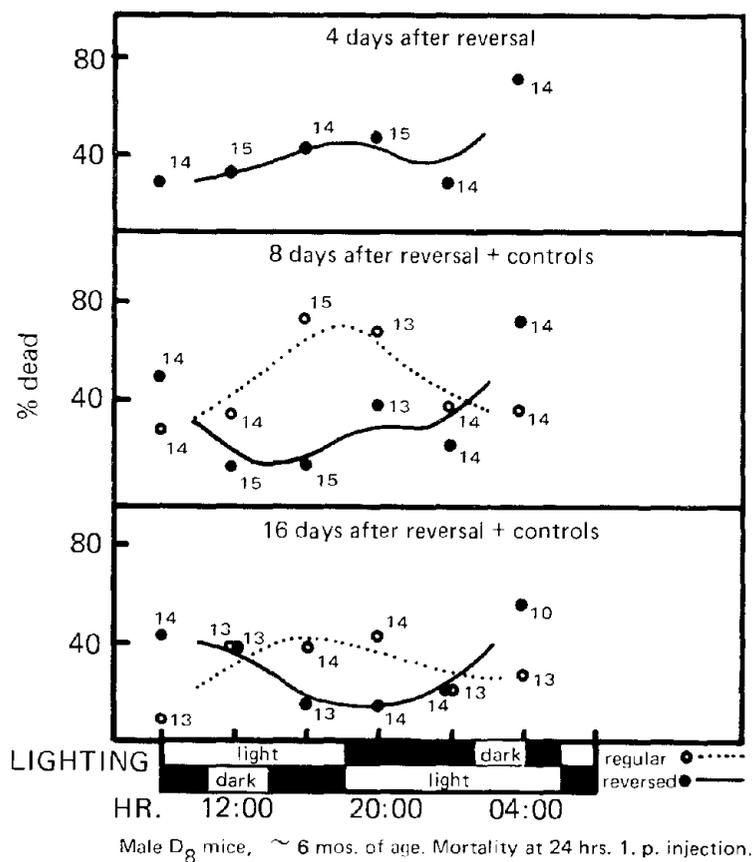


Figure 13. Gradual inversion of circadian susceptibility rhythm to ethanol after 12-hour phase-shift in lighting regimen. Total of 428  $D_8$  male mice.

of chronopharmacologic concepts to cancer therapy may follow two avenues, both of which appear promising:

1. The undesirable effects of the treatment on the host may be minimized by timing of the treatment according to the host's susceptibility cycle to a therapeutic agent. This may lead to lesser undesired effects by a given dose or allow an increase in dose with increased effect upon the tumor but without unacceptable side effects.

2. Possible circadian or other rhythms of tumor growth and metabolism may lead themselves to a treatment schedule adjusted to the tu-

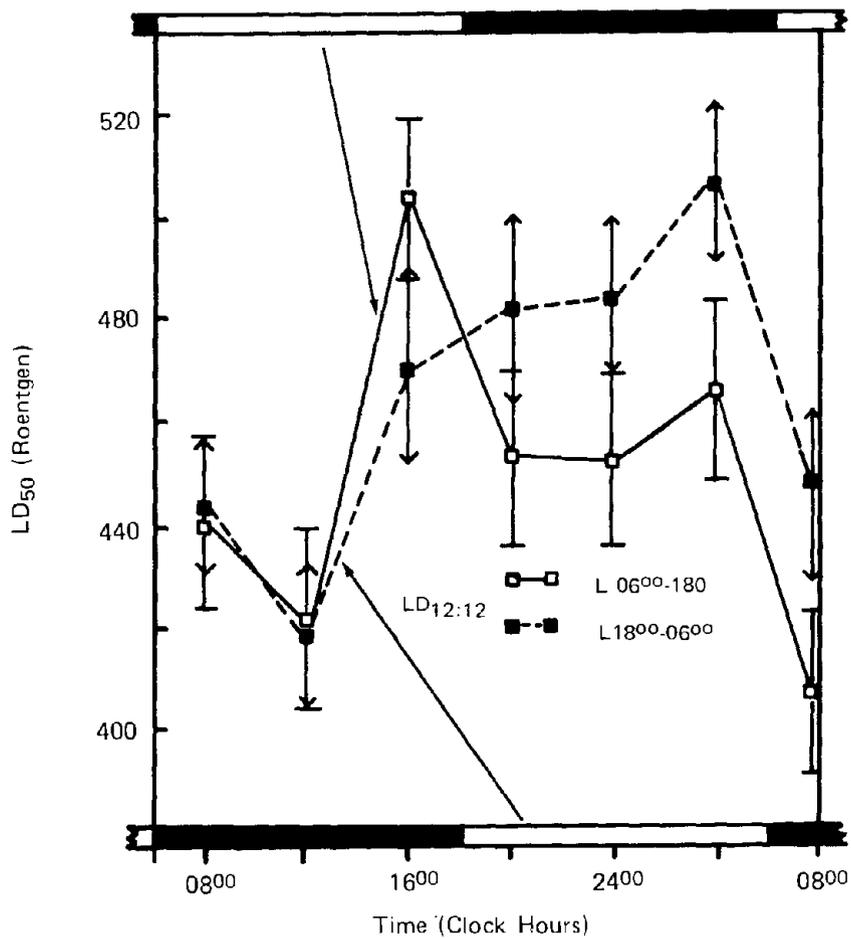


Figure 14. Comparison of  $LD_{50}$  (roentgens) as it changes along the 24-hour scale in C-mice on two lighting regimens.

mor's time structure whenever such a phenomenon can be ascertained and monitored in a human malignancy.

Finally, in an ideal approach, both the time structure of the host and of the tumor may be used for an optimal chronotherapy of neoplasia.

If a tumor does not show a detectable rhythm in metabolism and/or cell division, chronotherapy may be limited to the improvement of host tolerance but even in this limited application may represent a significant improvement over all existing treatment schedules established without regard to the organism's time structure.

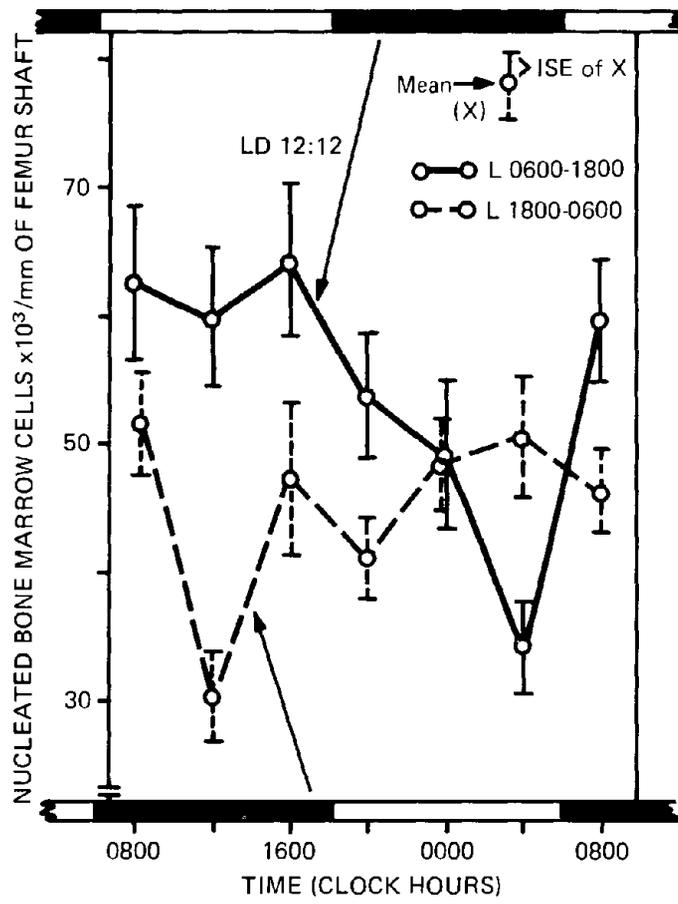


Figure 15. Bone marrow depression by whole body x-radiation in relation to circadian system phase at time of exposure of adult male C mice to single dose (350r).

Alternatively, even in an apparently non-circadian periodic tumor, an attempt could be made to induce and maintain a tumor rhythm by synchronization of the randomly dividing tumor cell population by physical or chemical agents. The induction of a rhythm in tumor metabolism and tumor growth may allow a chronotherapeutic approach with the treatment timed to make the most sensitive state of the tumor rhythm coincide with the most resistant state in the sensitivity cycle of the host. If periodicities of a tumor can be detected and mapped as, e.g., in the case of certain human breast cancers, multiple myelomas, leukemias or in animal tumors, mouse breast cancer, rat sarcomas, or some forms of Ehrlich ascites tumor, both host and tumor rhythms have to be considered for optimal chronochemotherapy.

If the sensitivity cycles of host and tumor for a specific agent are differently timed, treatment can be instituted at a time of high resistance of the host and high susceptibility of the tumor. If this ideal condition does not exist and if the sensitivity of host and tumor to a given agent is high and low at about the same time, acrophase manipulation of host or tumor may be attempted. This may be achieved for the host, e.g., by change of lighting regimen, change of living pattern, change in feeding time, administration of certain drugs (e.g., corticosteroids) etc.

In the tumor, a time shift may be attempted by, e.g., chemotherapeutic agents or physical agents like irradiation. The same agents conceivably might be used for the synchronization of a circadian periodic tumor which may show a period consistently different from 24 hours and thus free-runs from the astronomic day-night cycle and the 24-hour synchronized host rhythms. However, in the observation of sensitivity-resistance cycles and especially in the application of this concept to prolonged treatment with repeated courses of potentially toxic agents, possible treatment effects upon the circadian system of the experimental animal or of the patient have to be kept in mind. As shown by Scheving et al, treatment with cytosine arabinoside, a drug widely used in the treatment of certain hematologic malignancies, does phase-shift the circadian cycle of frequency of cell division in certain tissues of the mouse. Thus, a second dose of the drug given on the following day at the same clock hour will find the animal at a different circadian system stage and on a statistical basis will find the majority of cells in a given tissue undergoing cell division in a different stage of their mitotic cycle than on the day before. An organism exposed to a potentially noxious stimulus also may respond with free-running of certain (but not necessarily all) circadian periodic functions as shown in Figure 16. In this case a patient undergoing radiotherapy for metastatic breast cancer developed during the time of the treatment a circadian rhythm in sodium excretion which was slightly but consistently different from 24 hours and thus became free-run-

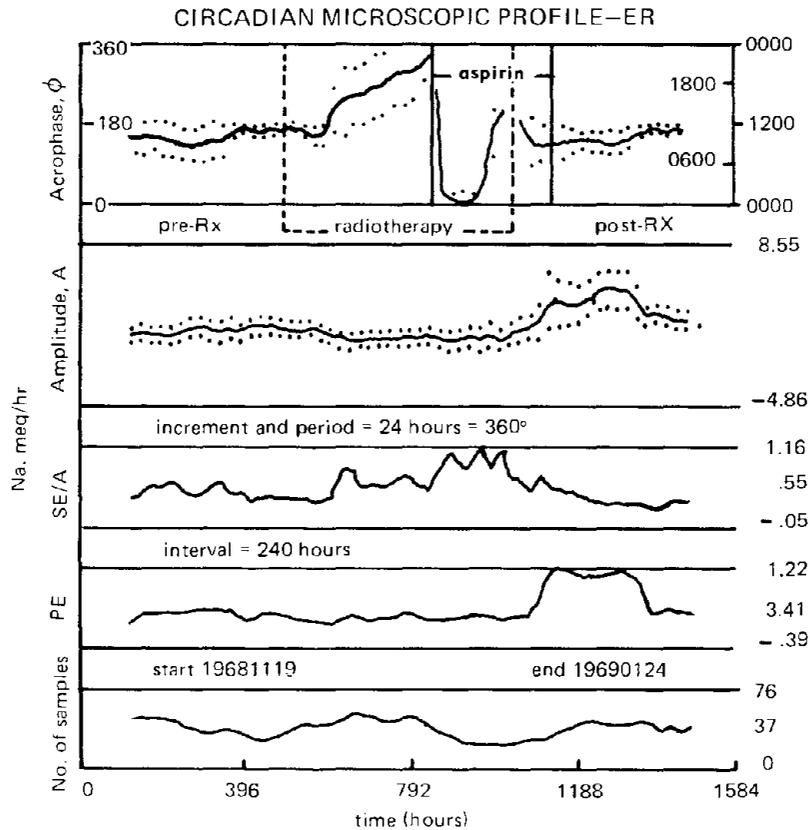


Figure 16. Chronobiologic serial section of urinary sodium excretion in a patient receiving radiotherapy after radical mastectomy. Note drastic changes in sodium acrophase during radiotherapy and increase in rhythm's amplitude after treatment.

ning of the astronomic day-night cycle with the acrophase every day occurring at a different clock hour. Considering other body functions, e.g., the body free-running function and its underlying mechanisms for radio-resistance, whether or not this condition will alter the patient's circadian cycle in susceptibility to radiation, is a question which could not be followed in this case.

The presence of malignant disease in itself may change an organism's time structure and its capability to phase shift circadian periodic body functions after a change in synchronizer phase. The influence of a transplantable malignant tumor, the L1210 acute leukemia upon the time

structure of the host and on its amenability to phase-shift by a 180° change in the lighting regimen was explored recently in a series of experiments when 408 male BDF<sub>1</sub> mice were housed in two periodicity laboratories on a lighting regimen of LD12:12 with L hours 0600 to 1800 and D hours 1800 to 0600. Additional animals carrying L1210 leukemia were housed in both rooms. The leukemia was transplanted to new carriers every sixth day. After two weeks on this regimen, the lighting schedule in one room was shifted to 180° (12 hours) to LD12:12, L 1800 to 0600 and D 0600 to 1800. The lighting regimen in the other room remained unchanged.

After two weeks of exposure of the animals and of the tumor carriers in the one room to the phase-shifted synchronizer cycle, half of the mice received 10<sup>4</sup> L1210 leukemia cells i.p. The other half of the mice received saline. Six days later, separate serially independent subgroups of mice on both lighting regimens, with and without tumor, had their rectal temperature taken and then were injected with 5  $\mu$ c of <sup>3</sup>H-Thymidine in four hour intervals beginning at 0800 of the first day until 0400 of the following day of the study. The animals were killed 15 minutes after <sup>3</sup>H-Thymidine injection. Blood was collected for complete blood counts and for serum corticosterone determinations by fluorometry. The <sup>3</sup>H-thymidine uptake was studied (as relative specific activity: cpm/mcg DNA) in L1210 tumor cells obtained from ascitic fluid in splenic tissue and in liver tissue.

Least squares fit analysis showed circadian rhythms for each of these functions in the non-leukemic mice and in the tumor-bearing animals, Figures 17-23.

In the animals exposed for 21 days to the 180°-shifted regimen, the expected phase-shift of the circadian rhythm in serum corticosterone levels, Figure 17 and in body temperature, Figure 18, was found. A partial phase-shift in the circadian rhythm of circulating lymphocytes occurred in the healthy and in the tumor-bearing animals, Figure 19. A phase-shift was recognizable in the non-leukemic animals but not in the leukemic mice in the circadian rhythm of <sup>3</sup>H-Thymidine uptake in splenic tissue, Figure 20, and in the circadian rhythm in circulating monocytes, Figure 21. The rhythms of <sup>3</sup>H-Thymidine uptake in liver tissue and in the number of circulating neutrophil leukocytes in non-leukemic mice appear to go through transient cycles with loss of rhythm detection while the rhythmometrically verified circadian rhythms of these functions in leukemic mice remained unchanged, Figure 22a, 22b. The tumor itself showed a highly significant circadian rhythm in <sup>3</sup>H-Thymidine uptake which was not amenable to phase-shift under the conditions studied, Figure 23. These data indicate:

1. an alteration in the circadian synchronized animal of certain cir-

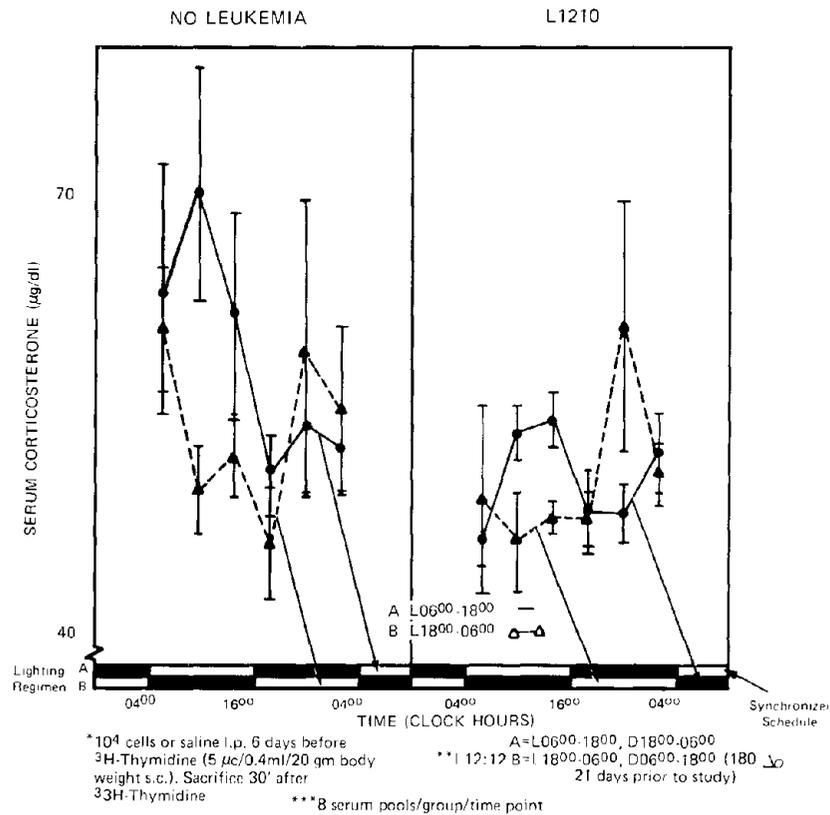


Figure 17. In 408 BDF1 mice with and without L1210 leukemia\* on two lighting regimens\*\*.

adian periodic body functions in the presence of a transplantable rapidly growing malignant tumor,

2. an alteration in the hosts' ability to adapt the acrophase of some but not of other circadian periodic functions in the presence of such a tumor to an abrupt 180°-shift in synchronizer phase and, finally.

3. the presence of a circadian rhythm in radiothymidine uptake in the tumor itself in spite of a cell generation time reported by others as being around 12-14 hours and

4. the lack of appreciable phase-shift of this tumor rhythm 21 days after shift in synchronizer phase and in spite of the phase shift of certain body functions (e.g., the adrenal cycle) in the host.

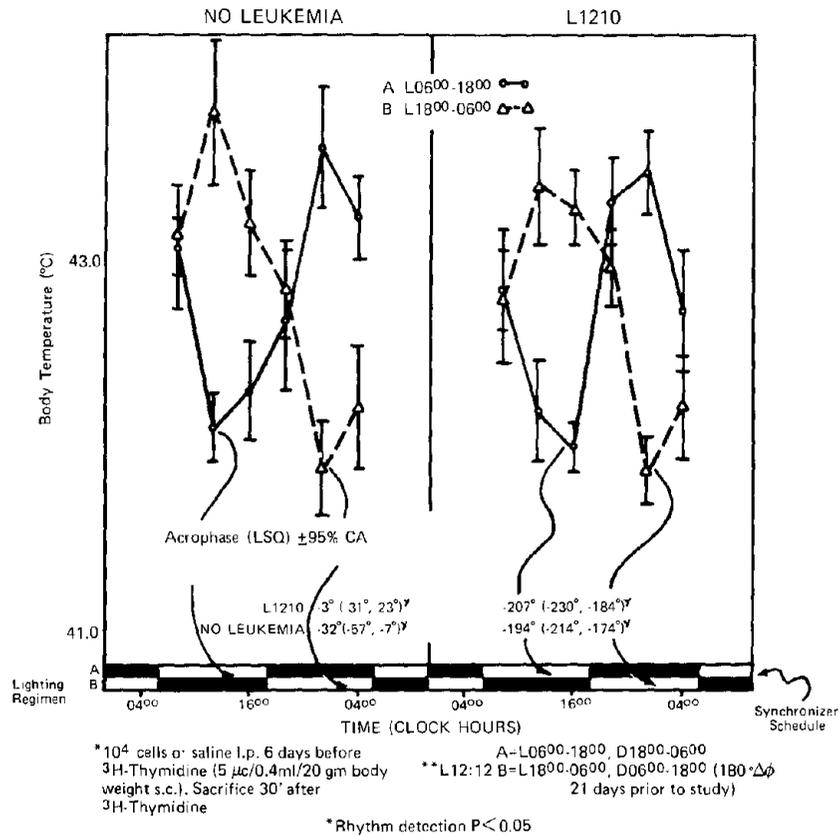


Figure 18. Circadian rhythm in body temperature in 408 BDF1 mice with and without L1210 leukemia\* on two lighting regimens\*\*.

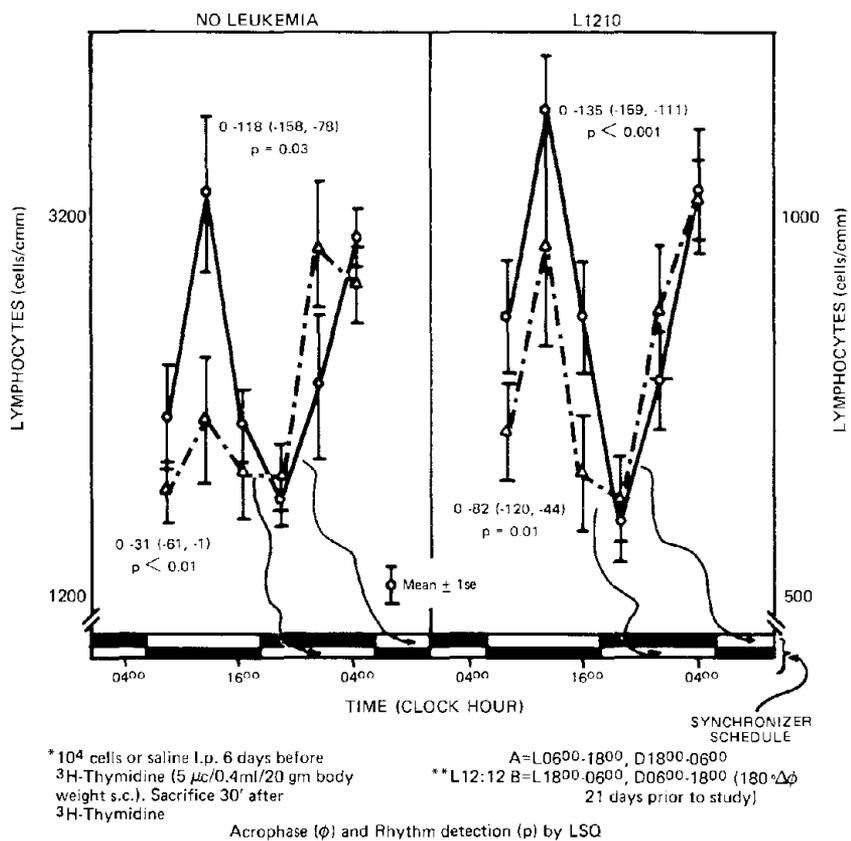


Figure 19. Circadian rhythm of circulating lymphocytes in blood of BDF1 mice with and without L1210 leukemia\* on two lighting regimens\*\*.

Incomplete phase-shift in tumor-bearing ( $\Delta\phi = 53^\circ$ ) and non-tumor bearing ( $\Delta\phi = 87^\circ$ ) mice.

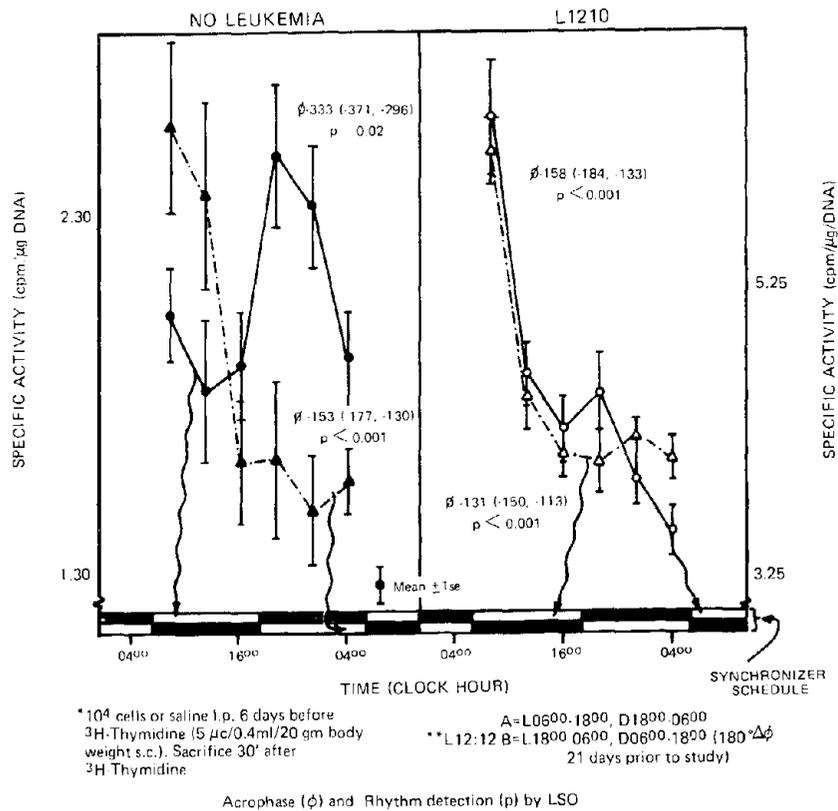


Figure 20. Circadian rhythm of incorporation of <sup>3</sup>H-Thymidine in spleens of BDF1 mice with and without L1210 leukemia\* on two lighting regimens\*\*. Absence of phase-shift in tumor-bearing mice.

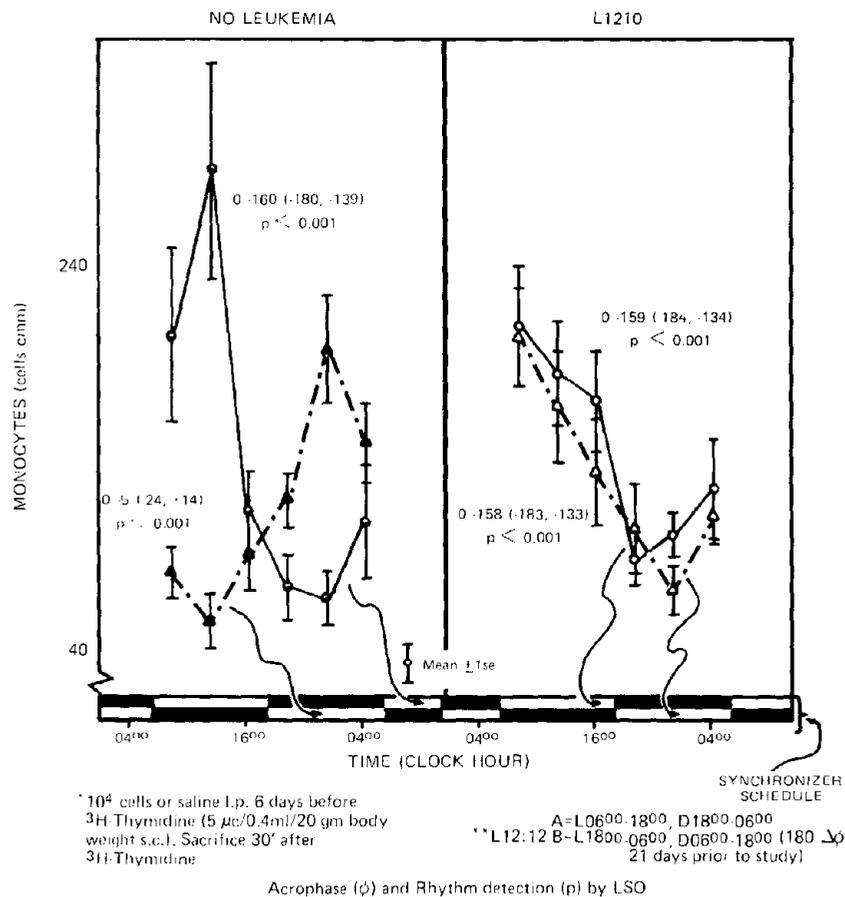
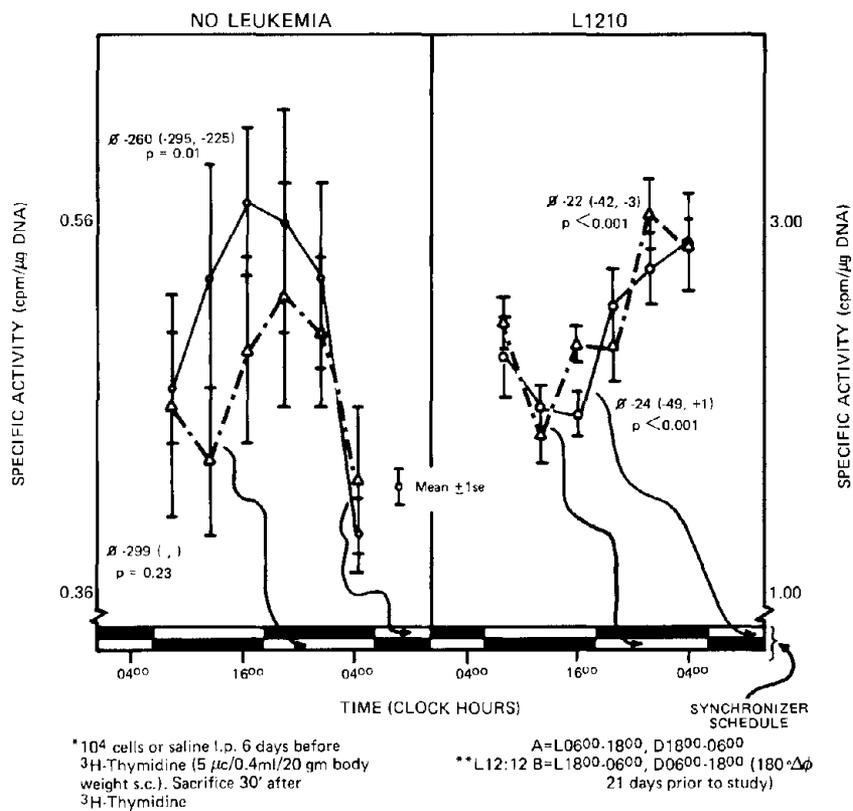


Figure 21. Circadian rhythm of circulating monocytes in blood of BDF1 mice with and without L1210 leukemia\* on two lighting regimens\*\*. Absence of phase-shift in tumor-bearing mice.



Acrophase ( $\phi$ ) and Rhythm detection ( $p$ ) by LSQ

Figure 22a. Circadian rhythm of incorporation of <sup>3</sup>H-Thymidine in livers of BDF1 mice with and without L1210 leukemia\* on two lighting regimens\*\*. Absence of phase-shift in tumor-bearing mice.

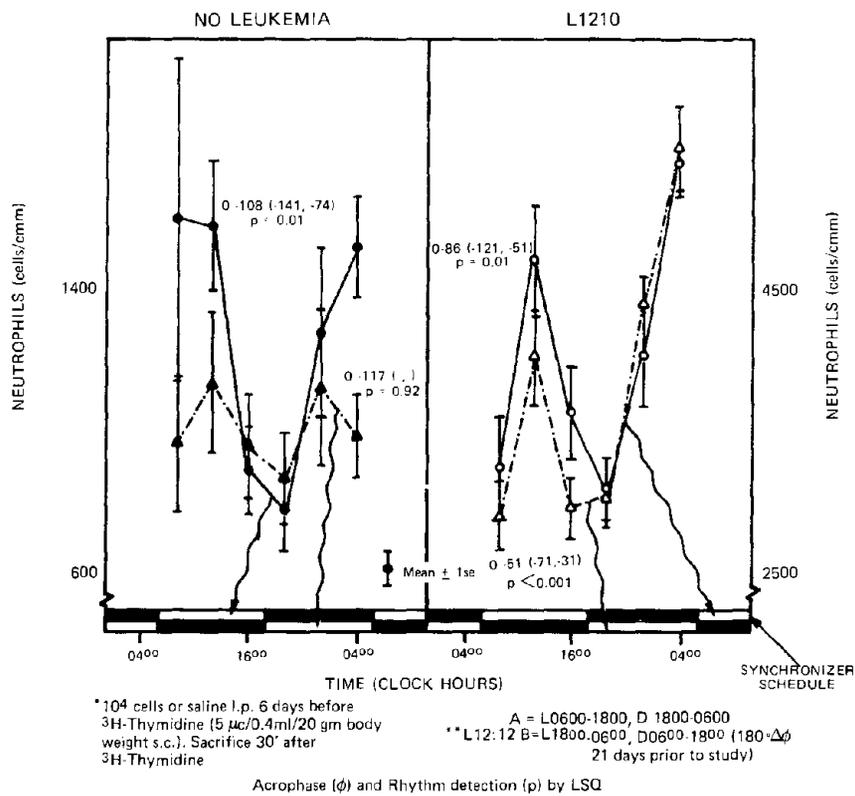


Figure 22b. Circadian rhythm of circulating neutrophils in blood of BDF1 mice with and without L1210 leukemia\* on two lighting Regimens\*\*. Absence of phase-shift in tumor-bearing mice.

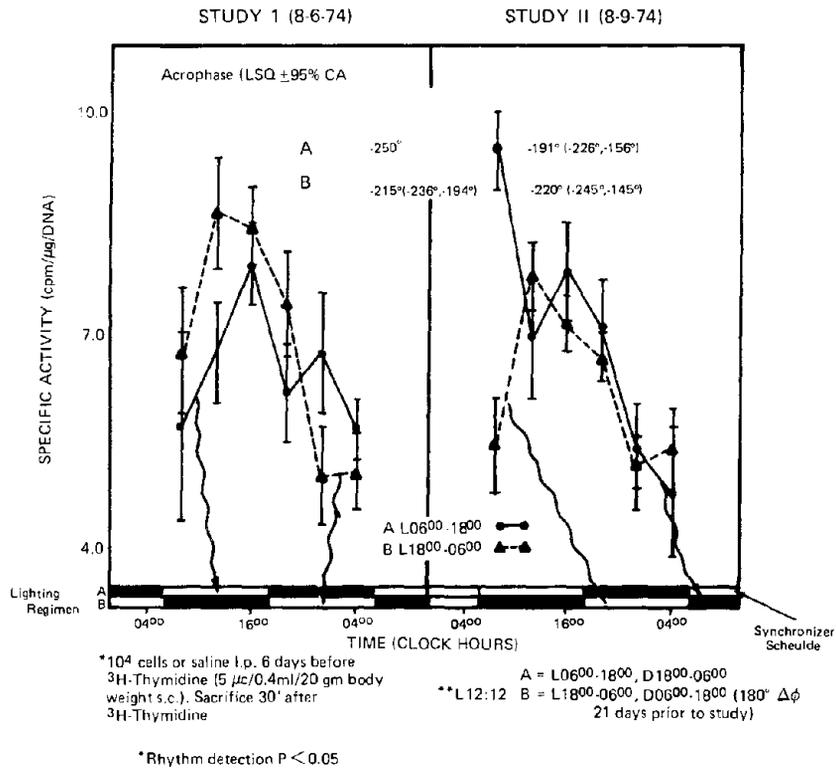


Figure 23. Circadian rhythm of <sup>3</sup>H-Thymidine incorporation in L1210 leukemia cells\* in ascites of BDF1 mice. 21 days after 180° (12 hr) shift in lighting regimen\*\*.

**CHRONOBIOLOGY AND HOW IT MIGHT APPLY  
TO THE PROBLEMS OF SHIFT WORK:  
DISCUSSION I**

*Lawrence E. Scheving\**

The temporal structure of most living things is a highly organized composite of many rhythms ranging in frequency from cycles per second to cycles per year and even to the cycle of a lifetime. Within recent years, there has been one rhythmic frequency which has been investigated intensively, and that is the circadian. A circadian rhythm implies that any variable (psychological, physiological or biochemical), if adequately monitored, can be seen to fluctuate and a high and low value can be demonstrated once each 24 hours if the rhythm is in the synchronized state or once approximately every 24 hours if it is in the desynchronized or free-running state.

For both man and animal, this frequency has evolved secondary to the daily rotation of the earth and is of adaptive value, since it serves as the mechanism which permits the organism to adjust in an orderly manner to the gradually changing environment such as those changes accompanying the different seasons.<sup>17</sup>

In the case of the experimental rodent, the circadian system is strongly synchronized to the light-dark cycle of nature or to that of the laboratory.<sup>22</sup> Man, however, has evolved to the state in which the social routine is more apt to override the synchronizing effect of the light-dark cycle, or at least it plays a more dominant role in synchronizing the circadian system.

We do not deny that light may be playing an important role in the overall synchronizing process in the human, and hence the system might best be described as being socio-ecologically synchronized. The great majority of people within an industrialized society such as our own are very closely socially synchronized in that they eat approximately three

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\*Co-authored by E. L. Kanabrocki, U. S. Army Reserve; R. L. Brewer, U. S. Army Reserve; T. J. Bird, U. S. Army Reserve; and Dr. John E. Pauly, Chairman of the Department of Anatomy and Professor of Anatomy, University of Arkansas Medical Center, Little Rock, Arkansas.

meals per day at roughly the same time and sleep about six to eight hours per day, usually between just before midnight and 6 to 8 a.m. In a large majority of people, the crest in body temperature can be expected to occur about mid-afternoon; the maximum urine production will occur during the early part of the day; and blood steroids begin to increase prior to awakening (presumably to prepare one to cope with the trials and tribulations of the waking state). In short, the circadian system is geared to activity during the early part of the light (or diurnal) phase and to the beginning of sleep which usually occurs at approximately the mid-part of the dark (nocturnal) phase.

These fluctuations are not always apparent to us in the same sense that the respiratory or menstrual rhythm is; they only become overt when they are measured at frequent intervals over the 24-hour span. Because of their somewhat "invisible" nature, there is a tendency on the part of some to ignore them.<sup>15</sup> Those who do so unfortunately may rationalize that the fluctuations represent no more than minor variation around a daily mean, and consequently do not warrant the additional work and expense required to explore properly for their significance.

Coupled with this viewpoint is the fact that the concept of homeostasis still is being taught in medical school physiology courses.<sup>17</sup> The consequence is that the human system frequently is treated as if it were a machine and capable of enduring the same load, without adverse consequences, at all phases of its circadian system (or some would prefer to say, at all times of the day or night).

The modern shift worker falls victim to this erroneous thinking, since it is expected that his or her circadian system will withstand the same load and be equally efficient at all phases; or, even though one may recognize that the circadian system is not necessarily efficient at all phases, it is erroneously assumed by many that the individual will quickly phase-shift or adjust when subjected to the perturbation of shift work.

Since some scientists are unaware of the magnitude of circadian changes that occur over the 24-hour period, we shall begin by illustrating with a few examples of rhythmic variation occurring in man, following this with examples of phase-shifting obtained primarily from animal studies, and concluding with our view of how further exploration might be carried out.

#### *Examples of Circadian Variation*

We shall describe results obtained in 1969 and 1971 on a group of clinically healthy young men. The precise methods used to obtain the data for the 1969 group have been published previously;<sup>8, 9</sup> the data obtained in 1971 are essentially unpublished and, consequently, the methods need to be presented herein. (I might add that the methods of the second study were very similar to those of the first.)

The 1971 investigation was carried out using as subjects 12 presumably healthy, male Army reservists, many of whom were participants in the 1969 study. These reservists were participating in their required two-week annual training. All had college educations and were highly motivated volunteers who averaged  $27.5 \pm 1.9$  years of age (range 19 to 43). The sampling, at three-hour intervals over a 72-hour span, began on Tuesday, May 18, 1971 (the 1969 study also was conducted in May). This was three days after the subjects (residents of the Chicago, Ill. area) had arrived by airplane at Fort Sam Houston, Texas. Their flight did not involve a time-zone change.

During the three days prior to the beginning of sampling, no special effort was made to standardize the group beyond what the routine of Army life normally would accomplish; the men slept, worked and ate on almost identical schedules. Cots were set up in a large open barracks. All men were assembled in this room at 1500 on the first day of sampling and were instructed as to the procedures to be followed during the 72-hour sampling span.

At precisely 1600, they were told to empty their bladders so that the first urine collected at 1900 would represent a three-hour accumulation. Members of the group were asked to abstain from any unusual or strenuous activity during their waking hours (0700 to 2100). The subjects were told to remain in bed to rest and/or sleep between 2100 and 0700 except for the times of scheduled three-hourly sampling.

During the rest span, the room was quiet and darkened. The subjects were not restricted in their water intake except during the 30 minutes prior to sampling, but were required to abstain from food or liquids other than water between meals, which were scheduled at 0700, 1245 and 1645. Although only two subjects smoked, it was permitted as long as it was not done 30 minutes before taking the temperature.

The food was prepared according to a master menu of May 1971 as outlined by the Department of the Army Supply Bulletin, issued in October 1970. Whatever the subject ate was consumed at meal times, although the amounts consumed were neither standardized nor measured. Testing at all stations listed below adhered to the protocol and was supervised by one of us (LES or ELK).

Sampling began at 1900 when all subjects urinated into graduated cylinders, care being taken to see that exactly three hours had elapsed since the previous urine collection. Each man went to his cot and reclined for a minimum of five minutes with a thermometer placed under his tongue during the entire time. He then sat up on the edge of his bed and recorded his temperature. The following psychological and performance tests were performed by auto-rhythmometry: (1) mood, (2) vigor, (3) eye-hand coordination, (4) finger counting, (5) time estimation, (6) random

number addition, and (7) memory. (All of these tests have been described elsewhere.<sup>6</sup>) While still in the sitting position and after completing all of the above tests, he then took his own blood pressure (systolic and diastolic). The blood pressure was taken at the end of the tests so as to assure a reading each time after sitting in a comfortable position for about seven minutes (the time it took to do all of the previously stated tests).

Data were analyzed separately for each individual; in addition, the analytical results were pooled for presentation as a group phenomenon. Some of the data reported herein are presented in the classical chronogram form, and others as cosinor-analyzed data. Both are necessary so that the reader unfamiliar with the more sophisticated inferential statistical techniques may visualize the rhythms in a form with which he is more likely to be familiar, i.e., the chronogram. The cosinor analysis does, however, have the advantage that a great amount of data can be analyzed with the aid of a computer and rhythmic parameters such as acrophase (crest), mesor (over-all 24-hour mean), and amplitude (extent of change) can be statistically evaluated. The cosinor techniques have been described in detail previously<sup>5,6,9</sup> and will not be repeated here.

The chronograms illustrated in Figure 1 serve to illustrate the circadian variation seen for the group of 12 clinically healthy young men. In general, the data demonstrate that (1) the group as a whole is reasonably synchronized to its social routine, (2) the variations seen for the group are statistically significant, and (3) the variations are reproducible from one day to the next.

Figure 2, on the other hand, summarizes over the 72-hour span the approximate peak of the circadian cycle for temperature, radial pulse, and systolic and diastolic blood pressure as well as for all the psychological and performance data illustrated above as chronograms in Figure 1.

Figure 3 is an acrophase map of data obtained from the study done in 1969 on essentially the same group of Army reservists. This figure also lists the results of group rhythm detection by the cosinor method as well as the specific rhythmic variables and the range of change for each variable for the group along the 24-hour time scale. The variables represented are those found for vital signs, serum and urine. Other selected variables from both the 1969 and a 1972 study are shown as chronograms in Figure 4.

#### *Vital Signs*

From observation of the 1969 data in Figures 3 and 4, it is evident that on the average, temperature, radial pulse, systolic blood pressure and pulmonary function are synchronized in both frequency and phase, and all show a significant fit to a 24-hour cosine curve. The acrophases are seen around the middle of the activity span. The acrophase difference between diastolic and systolic blood pressure was great, with systolic blood pressure leading in phase by  $133^\circ$ , Figure 3.

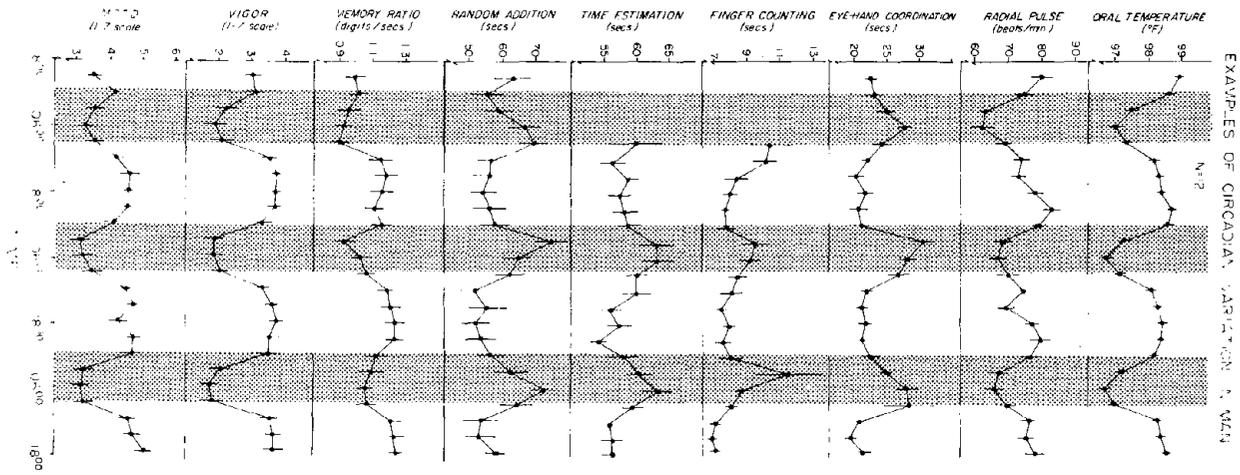


Figure 1. A series of chronograms demonstrating rhythmic variation over a 72-hour period in a group of 12 presumably healthy young men.

### ACROPHASE MAP OF 12 YOUNG SOLDIERS

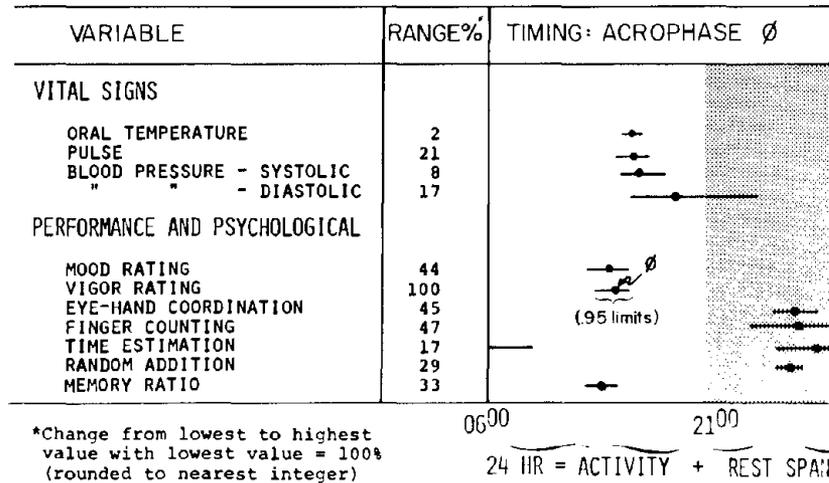


Figure 2. Acrophase (represented by a dot), approximating the peak of the circadian cycle, is shown with reference to the activity-rest schedule. Note that for all performance tests the acrophase represents the poorest performance.

In the 1971 study, the same phase relationship was seen, but the acrophase difference was only 32°, Figure 2. The significance of the differences between these two (systolic and diastolic) acrophases awaits further investigation. The extent of change in oral temperature over the 24-hour span was about 2°F, Figure 3. For pulse, the same change averaged 30% for the group, but the change was as great as 81% and as little as 21% for single individuals.

The range of change for systolic blood pressure was 12% for the group; whereas for the single individual it was as great as 57% and as small as 15%. Diastolic blood pressure changes for the group averaged 25% but were as great as 78% and as small as 14% for the single individual. At one phase of the circadian cycle, two of the 13 men in the 1969 study had blood pressure readings that might suggest at least diastolic elevation (150/108 and 148/96); the lowest readings recorded for these men were 122/80 and 94/70.

Pulmonary function varied for the group on the average of about 48% above the lowest value, and a single individual varied 165%; the least variation for any one individual was 46%, Figure 2. Although intraocular pressure invariably did not fit to a 24-hour cosine curve, there were statistically significant differences between time points (by *t*-test); the



CIRCADIAN VARIATION IN MAN

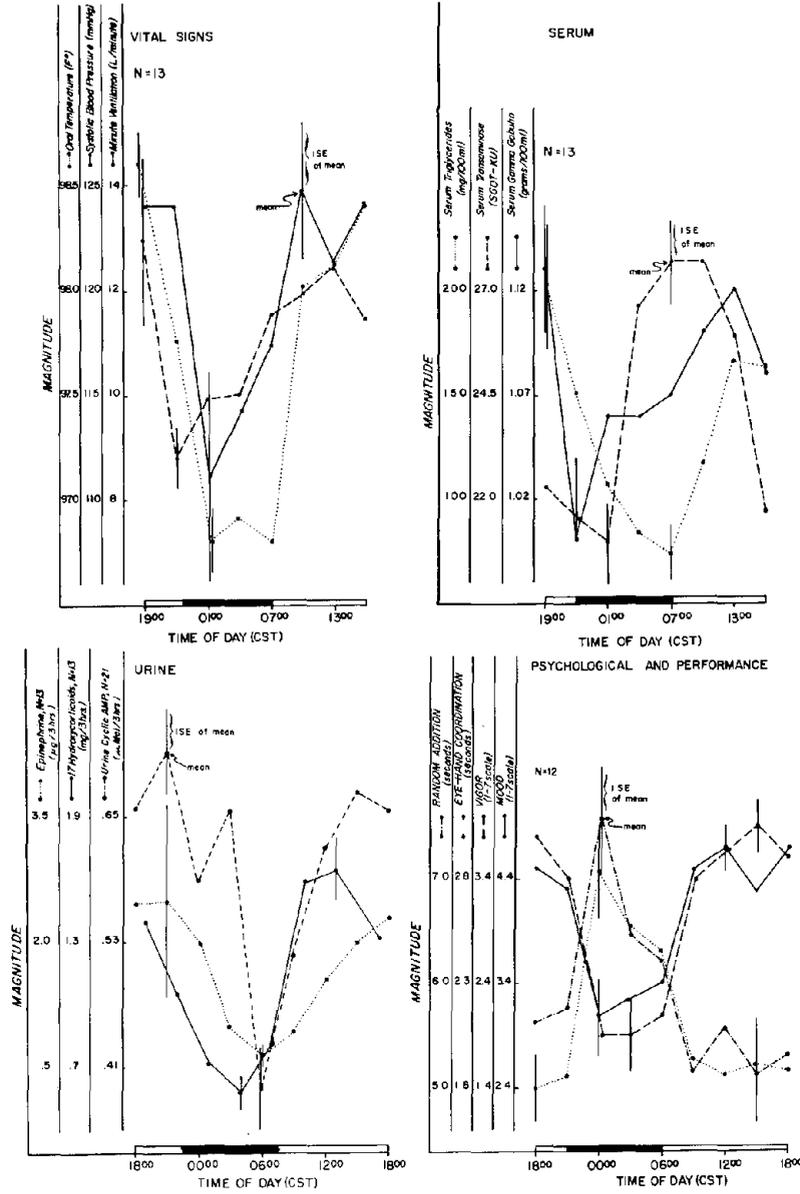


Figure 4. Circadian variation in man showing rhythms in vital signs, serum and urine variables, and physiological state. Note that for the random addition and eye-hand coordination tests, the peaks actually represent the times of poorest performance.

average range of change for the group was about 18%, the maximum range for any one individual was 85%, and the minimum was 18%, Figures 3, 4. The intraocular pressure in one presumably healthy man who had no symptoms of disease reached "pathological" readings for both eyes during one phase of the circadian system, while at other times the same man had values that were classified within the "normal" range. While any reading above 20 millimeters of mercury is often considered abnormal, this man's value varied from 17.3 to 29 mm of mercury. The occurrence of daily variation in intraocular pressure of both glaucomatous and normal eyes has been reported earlier.<sup>1,4,10</sup>

#### *Serum*

Of the 23 variables listed, all demonstrate by mean cosinor a group rhythm statistically significant at or below the 5% level, Figures 3, 4. Exceptions, not listed herein, were cholesterol and CO<sub>2</sub> content. It might be mentioned that for a few individuals the 24-hour cosine curve did provide a satisfactory fit ( $p < 0.05$ ) even for cholesterol and CO<sub>2</sub> content. The acrophases for total protein, albumin, globulin, glucose, and triglycerides seem to be synchronized — in phase — occurred about the middle of the activity span. The acrophases for albumin/globulin ratio, lactic dehydrogenase 1, 3 and 4, and potassium all occur during the activity span; acrophases for alkaline phosphatase, transaminase, glucose, chloride and calcium all occur toward the end of the activity span, Figure 3.

It is interesting that for bilirubin, the extent of change over 24 hours for the group as a whole averaged 54%. One individual showed a change of 750%, whereas the minimum for an individual was 47%. The range of change for transaminase levels for the group was 31%; the maximum range of change for one subject was 85%, the minimum of 25% was seen in another subject, Figure 5. The same type of analysis might be applied to any of the serum variables, and Figure 6 demonstrates this for triglycerides.

#### *Urine*

When each individual series on 14 urinary variables was fitted by a 24-hour cosine curve and group results per variable were summarized by mean cosinor, all of the variables measured except creatinine revealed a group rhythm statistically significant at the 5% level, Figures, 3, 4. The group acrophases of the rhythms thus detected occurred around the middle of the activity span. As was the case for certain vital signs and serum constituents, there were large changes during the 24-hour period, Figures 3, 4. Creatinine showed a group change averaging 24%; yet one individual varied as much as 381%, the minimum variation being 21%. Similar observations were made for 17-OH-corticoids; the group average range of change was 136%, with a maximum of 424% and a minimum of 43%.

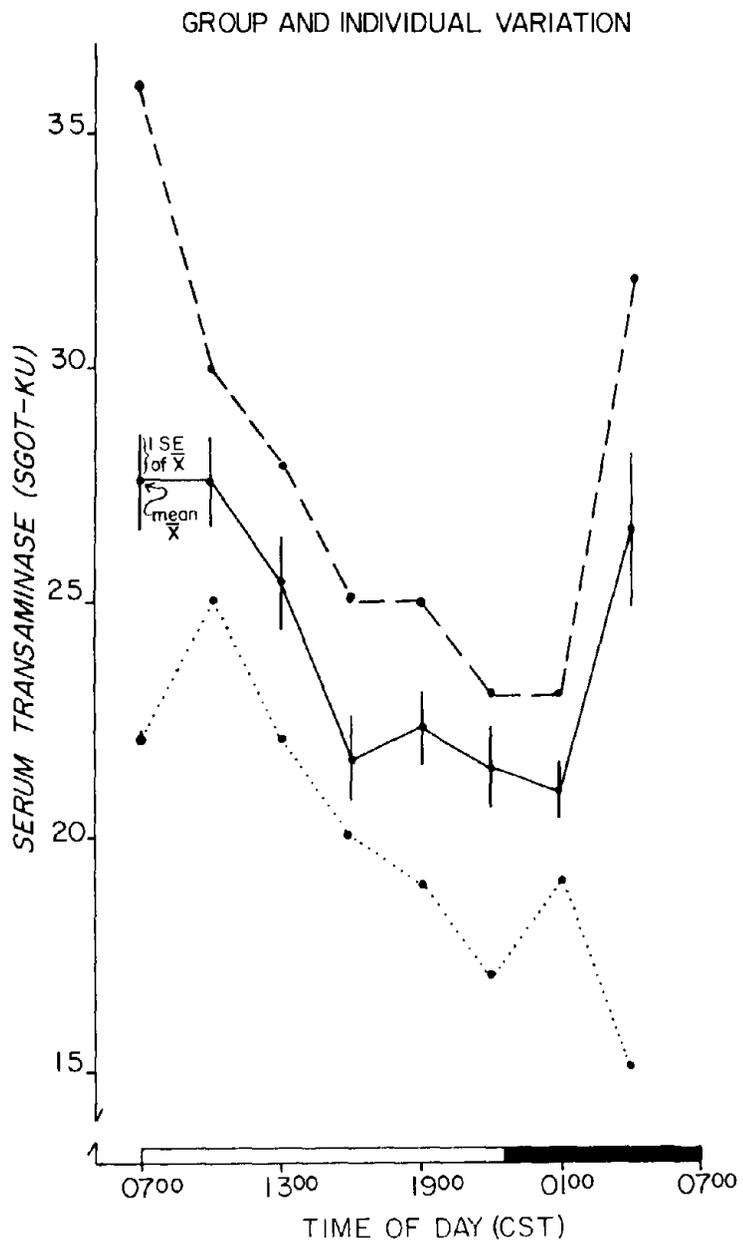


Figure 5. Individual and group variation in serum transaminase levels in young men consuming an identical diet.

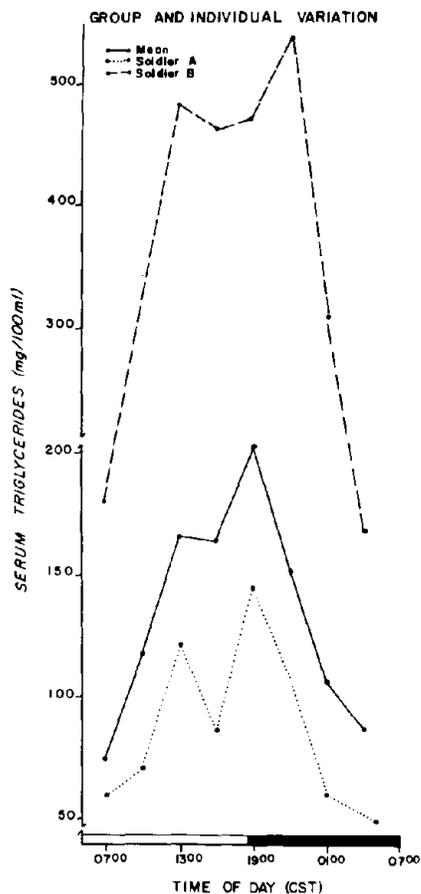


Figure 6. Individual and group variation in serum triglyceride levels in young men consuming an identical diet.

#### Performance

From analysis of the chronograms, Figures 1, 4, and the cosinor summary, Figure 2, it is evident that over a 72-hour span there are significant variations in eye-hand coordination. On the average, the range of change for the group during three successive 24-hour periods was 44%, 52% and 57%, respectively. However, on the first day, five out of 12 individuals varied over 100% in their ability to perform; the least variation for any one individual was 18%.

On the last day, two individuals varied over 200%, and the least variation among the 12 individuals was 62%. If one analyzes in a similar

manner the random number addition mental task, the group variation on the three different days was 28%, 48% and 40%, respectively, Figure 1.

On the first day, two individuals varied over 100%; the least amount of variation on this day for any one individual was 38%. On the second day the variation was as great as 180% for one subject and as small as 28% for another. On the third day a similar variation was observed in performing this task with one individual varying as much as 132%; the minimum variation for any one individual was 27%.

If one further analyzes random addition, we find that the poorest performances were recorded between 0000 and 0600 with the majority being recorded at 0600 on the first day. However, for some unknown reason, on the second day the time of poorest performance had shifted to midnight for the majority of the individuals; but on the third day it had shifted to 0300, Figure 1.

Recognition that peak performance cannot be tied to a specific clock hour is important; no one individual, however, demonstrated poorest performance between 0900 and 2100, and it was rare that a subject's performance peaked out as late as 2100.

#### *Comment*

One could continue to analyze in this manner the other physiological and performance variables, but we believe that the point has been made with the above two variables — that individuals in any population fall into three categories: (1) those having a high range of change for a particular variable; (2) those having a low range of change; and (3) those (possibly the largest group) who fall between these extremes. What, if anything, do the differences among the three categories imply as far as health is concerned?

It is conceivable that the amplitude of the rhythm may be important in evaluating the physiology of the man. It is noteworthy that a National Center for Health Statistics survey<sup>12</sup> reports that *on the average* human blood pressure varies during the day by no more than 3 to 4 mm of mercury. Although undoubtedly this statement is true — in average data — the variation is artificially reduced as we have shown repeatedly for our group of soldiers.

Such statistics can be very misleading, especially when it can be demonstrated that the variation in diastolic blood pressure in a presumably healthy resting subject can vary as much as 10 times the amount mentioned in the survey report.<sup>14</sup> It is unlikely that the wide fluctuation can be ascribed to experimental artifact. The same findings characterize other variables. Figures 5 and 6 illustrate the individual and group variations for the case of serum transaminase and triglyceride in soldiers consuming an identical diet. These examples clearly demonstrate a highly organized rhythmic pattern.

Because the circadian system is continually changing, the organism is a different entity biochemically at different circadian phase; and hence it will react differently to the same stimulus at different phases.

Figure 7 shows that when an organism is subjected to a potentially noxious agent, the response produced at one phase may be markedly different from that produced by the identical stimulus at another time.

In fact, the data illustrated herein demonstrate that the phase of the circadian system when the drug stimulus is given may determine the life or death of the organism. Other, less dramatic, examples could be cited to demonstrate that the degree of effectiveness of a drug or other stimulus is very likely to be circadian-phase dependent.<sup>7,11,13,18.</sup>

#### *Synchronizing and Phase-Shifting*

Normally, we think of the rodent as being synchronized to the light-dark cycle and man as being synchronized to his social routine, although there is strong evidence that the light-dark cycle also will affect synchronization of man. In the case of the rodent, it is easy to demonstrate that the light-dark cycle is the dominant synchronizer; because by inverting (abruptly or gradually) the light-dark cycle 180°, the phasing of many rhythmic variables, including body temperature, ultimately inverts. Figure 8 represents such inversion for the mitotic index of rat cornea.

The phasing of all variables is not so easily or quickly inverted; we know, for example, that the DNA synthesis rhythm in the bone marrow of mice takes a much longer period of time to invert. The consequence of unequal rates of phase-shifting for different variables is internal desynchronization during the adjustment phase.

Another example of phase-shifting is illustrated with the use of certain stimuli. For example, Figure 9 reveals that cytosine arabinoside (ara-C, a DNA inhibitor) induced a phase-shift for the corneal mitotic index in mice.<sup>16</sup> Forty BDF<sub>1</sub> mice, standardized to light from 0600 to 1800 alternating with darkness, were injected I.P. with 2.6 mg of ara-C in 0.2 ml of saline. Another 40 mice were injected only with 0.2 ml of saline. Injection of both ara-C and saline was made twice on the same day, at 1800 and 2100.

Two hours after the latter injection, subgroups of five mice from the control and experimental groups were killed at the intervals indicated on the graph. The mitotic index in the corneal epithelium in saline-injected animals showed the expected circadian rhythm with the timing corresponding to that found previously in similarly standardized animals. In ara-C injected animals, however, a phase-shift of about five hours became evident on the first day after administration of the drug. On the following day (the second day after treatment), the usual phase relationship between the mitotic rhythm and the ara-C treated animals (as well as

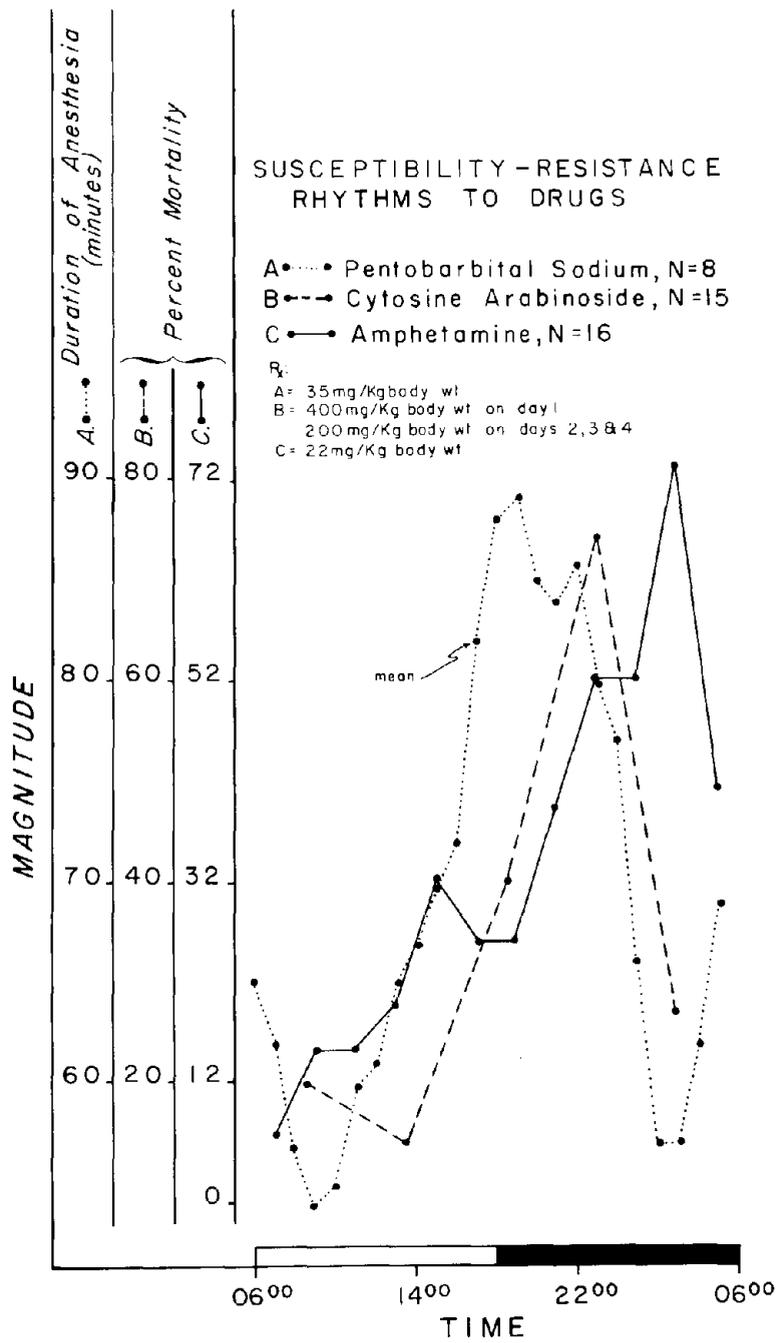


Figure 7. Circadian variation in susceptibility of rodents to pentobarbital sodium, cytosine arabinoside and amphetamine. For details, see Scheving, Vedral and Pauly<sup>19,20</sup> and Scheving et al.<sup>21</sup>

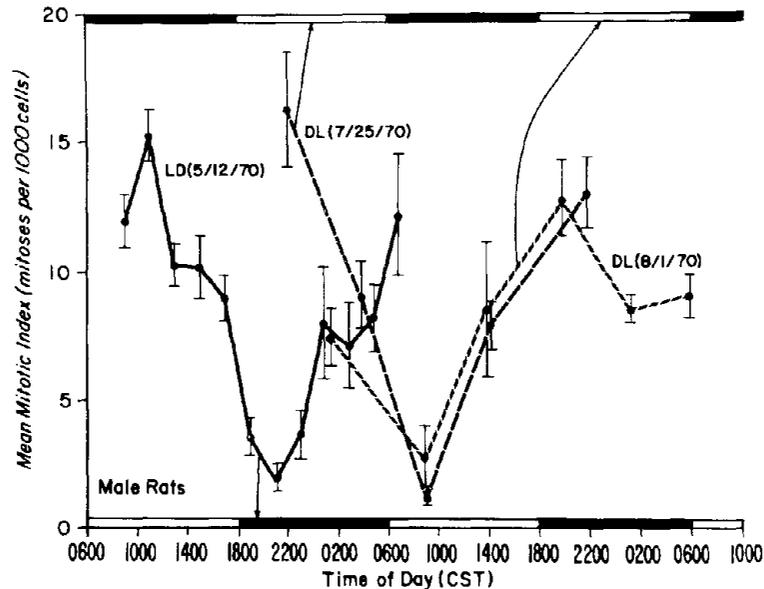


Figure 8. Comparison of rhythms seen in animals maintained in  $LD_{12:12}$  (light from 0600 to 1800) with those in animals maintained on  $DL_{12:12}$  (light from 1800 to 0600). Note that the rhythm reverses  $180^\circ$  after light periods are reversed. All photoperiods were artificially controlled.

the saline-injected mice) and the synchronizer cycle of alternating light and dark seemed to have been restored.

The rationale for performing the experiment dealing with the effect of ara-C on mitotic rate in corneal epithelium stems from a series of earlier experiments by us. It has been found that if ara-C is injected during the circadian phase when DNA synthesis is known to be high, there is no statistically significant decrease in the mitotic index that could be detected on the next day; the mitotic peak occurs at the expected time. However, if the same dose of ara-C is injected at the circadian system phase when the DNA synthesis rate is very low or just before it is to begin increasing, the mitotic index the next day, at the time of its expected circadian high, is instead very low.

The question asked was whether this failure to see the expected peak represented a phase-shift in the mitotic index rhythm or an actual depression in mitotic rate?

From an examination of Figure 9, it seems that the results obtained were due to a phase-shift of about four to five hours in the temporal place-

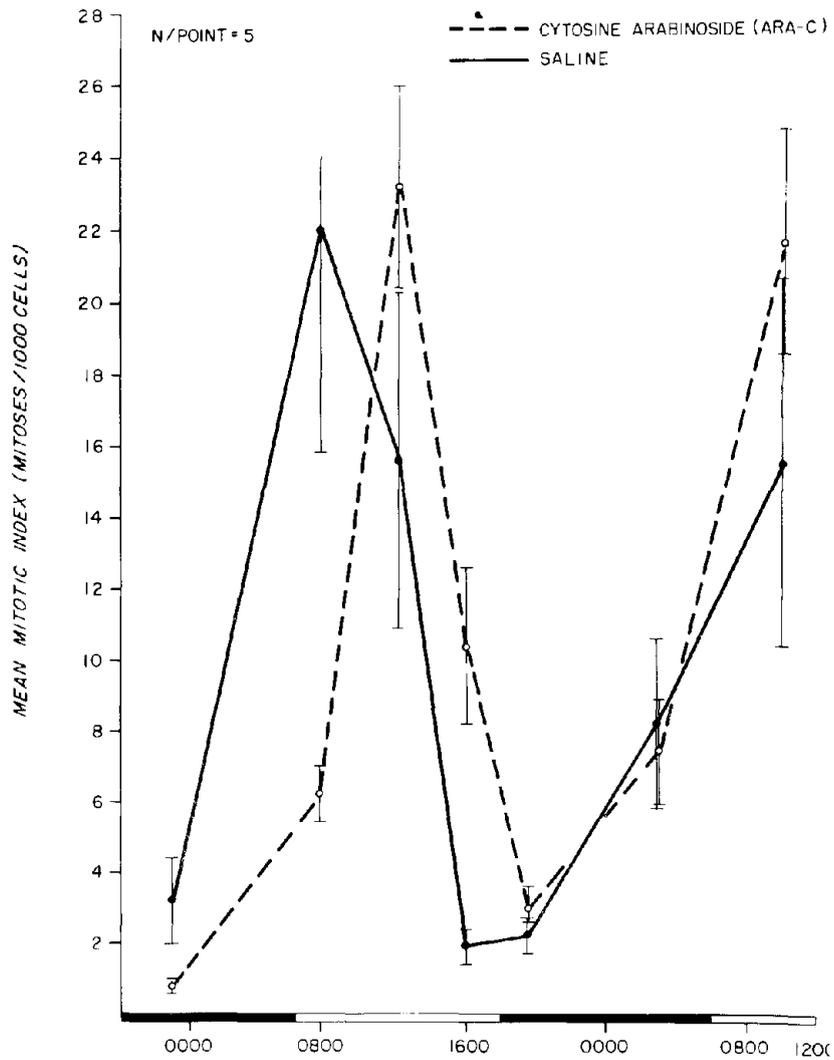


Figure 9. A four to five hour phase-shift in the mitotic index rhythm of mouse corneal epithelium is demonstrated when arabinosyl cytosine (ara-C) is injected during a phase of the mouse circadian system when the synthesis of DNA probably is minimal. Although not demonstrated here, there is no such phase-shift when the drug is administered at a time when one would expect a substantially higher rate of DNA synthesis or at the peak time of the mitotic index rhythm.

ment of the mitotic rhythm along the 24-hour time scale; consequently, single time-point sampling was misleading because it suggested a depression of mitosis when actually a phase-shift had taken place. We recognize, of course, that ara-C can depress mitosis in corneal epithelium if it is given at sufficiently high doses. However, the results presented in Figure 9 do clearly point out the complexity of evaluating the effects of drugs on mitotic activity and demonstrate, as well, the pitfalls awaiting those investigators who ignore the organism's time structure in the circadian or other time frequency ranges.

If one considers in a similar manner the drug which normally is thought to stimulate rather than inhibit DNA synthesis, namely isoproterenol (IPR), and gives it at the time when DNA synthesis is lowest, it has little effect on the mitotic index rhythm on the first two days but an effect is seen on the third day.<sup>2</sup>

If, however, the drug is administered when DNA synthesis is normally known to be high, an effect is seen in the mitotic index rhythm for three subsequent days. This is clearly illustrated in Figure 10; the solid line represents the natural rhythmic pattern in the mitotic index in corneal epithelium in control animals over a 68-hour span. The phasing is identical to what has been demonstrated many times for similarly standardized mice; the peak mitotic index consistently occurred at 0900 and the trough at 2100. The dashed line in Figure 10 represents the data obtained from mice injected with IPR at 0900. The mitotic index subsequently was monitored at four-hour intervals for a 68-hour span beginning at 2100 (12 hours after injection). The data revealed an advance in phasing of the peak of the rhythm by at least eight hours during the first day and by four hours on the second and third days of the experiment. The trough, unlike that in the ara-C study discussed above, did not phase-shift but did become more extended in time. Thus, the effect of this drug is more prominent on the wave-form of the rhythm.

Because of the shift of phasing, there is a statistically significant difference between control and IPR-injected animals at 0100 ( $p < 0.01$ ) and 0900 ( $p < 0.05$ ) on the first day. The same applies at 0500 ( $p < 0.05$ ) and at 0900 ( $p < 0.05$ ) during the second day. On the third day only one time point, 0500, demonstrated a statistically significant difference ( $p < 0.001$ ) in mitotic indices between IPR treated and control animals.

The dotted line in Figure 10 illustrates the data obtained when the mice were injected with IPR at 2100 and killed every four hours thereafter for 64 consecutive hours. The peak was advanced by four hours on day one. On the second day, there was a significant depression at 0100 ( $p < 0.05$ ) and 0500 ( $p < 0.01$ ), and a significant increase in mitotic index at 1300 and 1700 ( $p < 0.05$  in both cases). On the third day, there was a

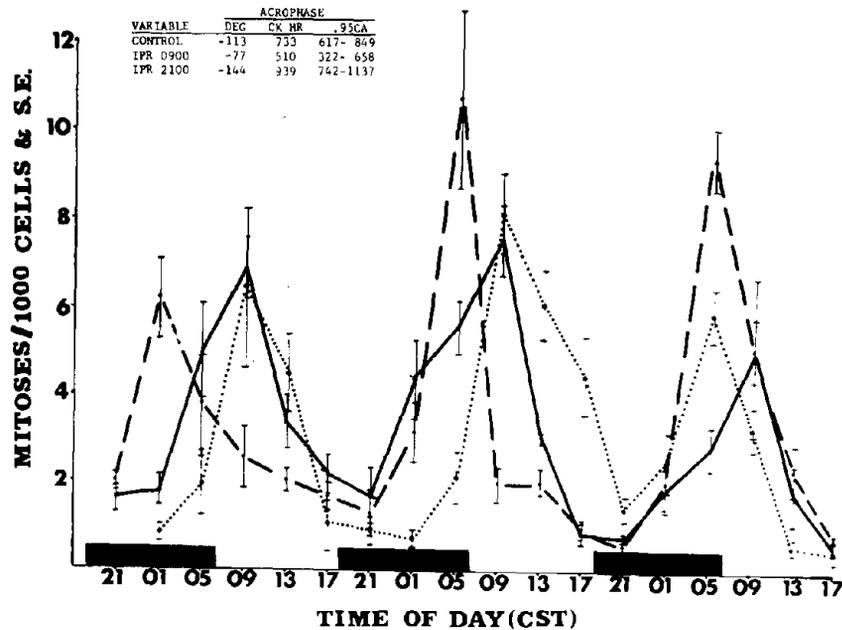


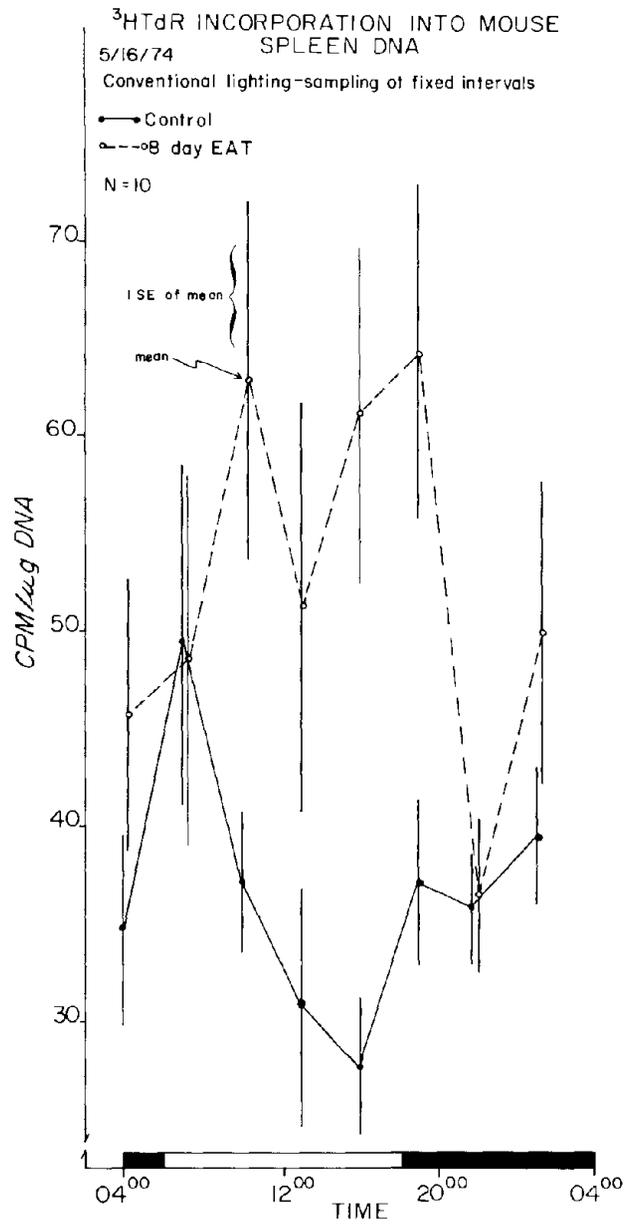
Figure 10. Mean mitotic index (number of mitoses per 1,000 cells and standard error of the mean) in the corneal epithelium of standardized mice injected with saline (solid line); injected with isoproterenol at 0900 and killed in subgroups of five mice every four hours beginning 12 hours (2100) after IPR injection (dashed line); and injected with IPR at 2100 and killed in subgroups of five mice every four hours (0100) after the IPR injection (dotted line). The points plotted are kill times.

significantly higher mitotic index in the IPR subgroup at 0500 ( $p < 0.05$ ). The over-all mean mitotic index for each group over a 68-hour period was  $3.2 \pm 0.6$  for the group of animals injected with IPR at 0900 and  $3.1 \pm 0.5$  for the group injected with IPR at 2100. There was no statistically significant difference between these two means.

Figure 11 is still another example of phase-shifting of a rhythm. In this case, the rhythm characteristic of DNA synthesis in the bone marrow of normal mice is dramatically phase-shifted in mice bearing an eight-day Ehrlich ascites tumor.

#### Discussion

The data presented demonstrate the relevance of chronobiology to the problems associated with shift work. They show that man unquestionably is rhythmic and that any response to perturbation will more than



*Figure 11. Typical circadian rhythm in DNA synthesis in the spleen of mice standardized to a light-dark cycle (light from 0600 to 1800) compared with the rhythm in similarly standardized mice bearing an eight-day transplanted Ehrlich ascites tumor (EAT). Note that the rhythm is phase-shifted in the tumor-bearing animals.<sup>3</sup>*

likely depend upon the phase of the circadian system at which it is encountered.

Obviously, it is not reasonable to expect one to perform as well at night as during the day. However, shift workers, as well as those who may have been rapidly displaced through several time zones, are put in the position of being expected to perform mental and physical tasks as efficiently with a "rest-time metabolism" as they normally are accustomed to doing with an "active-state metabolism." How effectively this information can be applied to the better management of shift work remains to be explored.

Admittedly, we do not have "hard" data on what the ultimate consequences of shift work are to the health and well-being of man. Such information simply is not available because adequate, in-depth studies have not as yet been made; this conference clearly serves to confirm this statement.

Since it is the basic rhythmic system that underlies the mechanisms by which the adjustment to shift work can be accomplished, it seems logical to recommend a chronobiological approach to the study of problems associated with shift work. Such an approach has an advantage in that certain performance, psychological, physiological and biochemical variables can be monitored during a span of shift work, and one can quantitatively demonstrate what is happening to the variable.

In undertaking a study into the effects of shift work on biorhythms, one must not select only one variable (such as body temperature which phase-shifts comparatively rapidly) to monitor and to interpret what is happening.

A multi-variate approach is essential. The multi-variate approach is necessary because we have found from our own studies on phase-shifting that some rhythmic variables shift rapidly while others are quite slow. Consequently, one can assume that at least some internal desynchronization does occur between variables which may or may not be interdependent. When such studies are undertaken they should be designed so as ultimately to include representative groups of different ages and sexes, and attention must be given to the subjects' shift work histories and also to the types of work performed (physical or mental). An initial study conceivably could concentrate on a select population and preferably one selected on the basis of what the consequence of error in performance might be. Examples of such populations are air controllers and pilots.

To ignore rhythmicity in evaluating shift work, in the light of the evidence, cannot be defended on any basis. However, one must recognize that the problems of logistics, consent of workers, management, unions, etc., undoubtedly are major obstacles to carrying out adequate studies. We do not believe, however, that these problems are insurmountable;

but we do strongly feel that anything less than carefully designed long-term cooperative studies would be apt to end as an exercise in futility.

If limited funds are available, an alternate first approach might be to carry out carefully designed animal studies aimed at evaluating the effects of repeated phase-shifting on the life span. Already some evidence exists to suggest that repeated phase-shifting shortens the life span of mice. For details of this, see Halberg as well as Hayes (both reporting in this symposium). We believe that several laboratories should investigate simultaneously this phenomenon in animals and that the overall study should be a coordinated effort. If such alteration in life span in experimental animals due to phase-shifting can be demonstrated conclusively, such studies would be quicker and also would serve as a firm basis for exploring the same problems in man.

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**CIRCADIAN RHYTHMS IN DRUG EFFECTIVENESS  
AND TOXICITY IN SHIFT WORKERS:  
DISCUSSION II**

*Martin C. Moore Ede*

A lot of very interesting information has been presented to us this morning. Dr. Haus, in particular, has given some important illustrations of his contribution to our understanding of the effect of circadian variations in the susceptibility and effectiveness of drugs. There clearly are many problems and much to do in this field of research. We understand very little about the mechanisms which underlie these phenomena and obviously much more work has to be done.

I wish to talk about the nature of the circadian timing system and to consider the implications of our current understanding of the system for the way in which therapeutic drugs and toxicological substances are handled in individuals who are subjected to shift work.

Shift workers, like everyone else, receive a wide variety of drugs and medications during their lifetime and, in addition, are exposed to a wide variety of toxicological hazards. Gradually, we are gaining information, as Dr. Haus showed in his presentation, on the circadian variations in effectiveness and toxicity in drugs. However, these studies have been performed largely in steady-state conditions, that is, conditions where the human subjects and animals under study were synchronized to a rigid 24-hour environment and had remained synchronized through most of their recent history.

We get into a whole new order of complexity when we start considering the transient changes that occur in individuals subjected to frequent phase-shifts in their environment. One, unfortunately, cannot go very far in understanding these transient changes with only the data collected from individuals in steady-state conditions. It will be necessary to understand what are the transient phenomena that occur in the circadian variations in drug absorption, metabolism and excretion before we can make any rational judgments about the best dosage schedules to use in shift-working individuals.

Such transient phenomena in circadian systems have been well demonstrated for various physiological functions. It has been shown that, when the environmental synchronizing functions are phase-shifted, the various monitored physiological functions in any advanced multicellular animal tend to take different lengths of time to resynchronize with the new phase of the environmental zeitgebers. Thus, there is a period of temporary internal desynchronization.

Such internal desynchronization is even more pronounced when the various zeitgebers in the environment occur at conflicting phases of the circadian day. In shift workers, social cues in the environment may be separately phased from such cues as feeding patterns and this will confound the problem of repeated phase-shifts of environmental variables.

To develop a firm scientific basis for analyzing these transient phenomena and for predicting their effects on circadian rhythms of drug effectiveness and toxicity, it is worth reviewing for a moment our understanding of the organization of the circadian timing system. It has become readily apparent that the circadian timing system in advanced multicellular animals such as man is not a single homogeneously oscillating unit. Instead, we are dealing with some sort of multi-oscillator system.

In Figure 1 are summarized three possible models of the circadian timing system in multicellular animals. Each of these models can account for the phenomenon of internal synchronization of circadian systems in multicellular animals and at the same time is compatible with the known

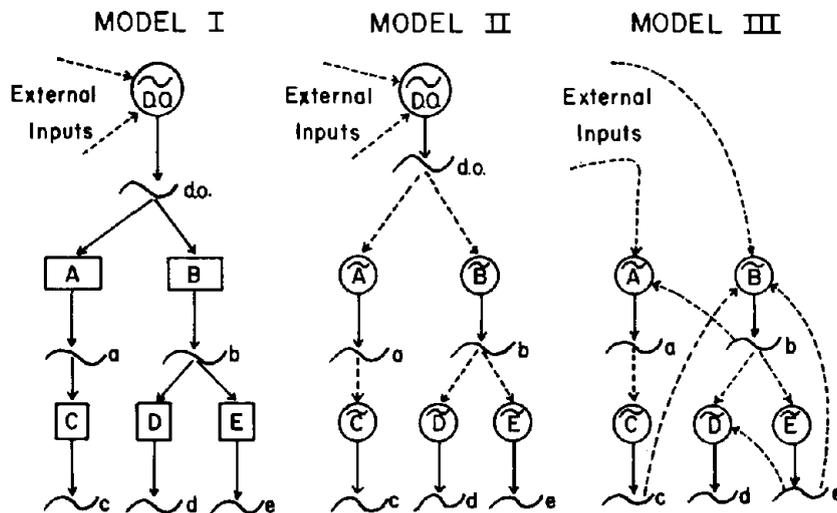


Figure 1. Alternative models of the circadian timing system. Model I is a single oscillator system while the other models are hierarchical (Model II) and non-hierarchical (Model III) multi-oscillator systems.

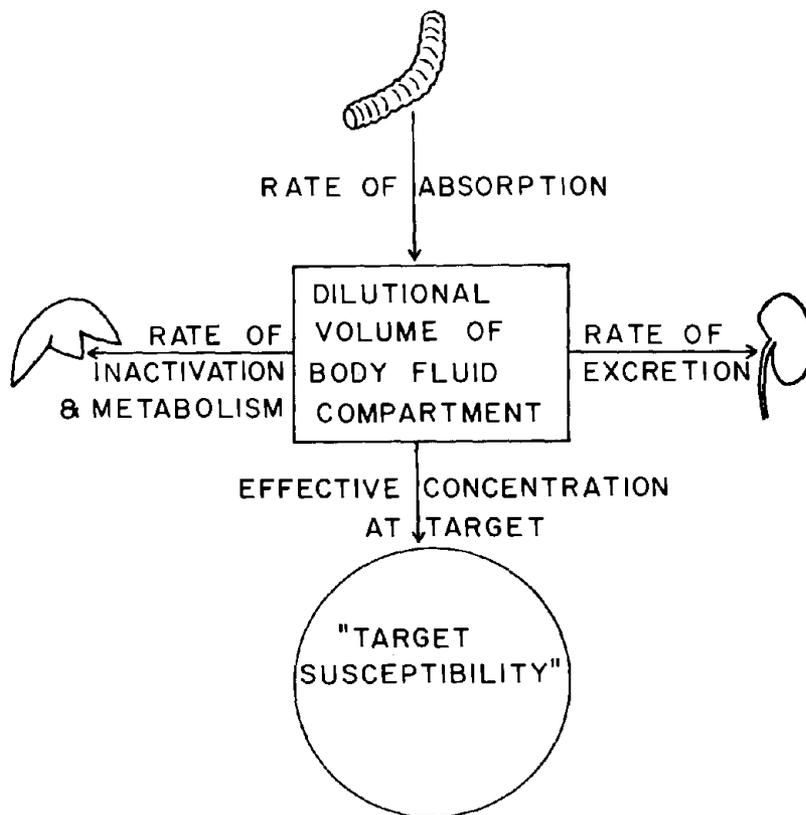
responses of the circadian timing system of environmental time cues. Variants of these models and combinations of their features also are possible, but the models presented in Figure 1 were selected because they emphasize the contrasts between the various viable oscillator systems.

The various cellular tissues of the body are labelled as A, B, C, . . . , etc. In Model I there is postulated a driving oscillator (D.O.) which forces a circadian oscillation in the various functions of the passively oscillating tissues. In Models II and III, however, we are dealing with multi-oscillator systems in which each body tissue can act as a potentially independent oscillator. These are normally synchronized with one another, either in a hierarchical manner with a driving oscillator (D.O.) acting as a pacemaker (Model II) or as a non-hierarchical system with the internal synchronization achieved through positive and negative feedback (Model III).

There is now considerable evidence that we are dealing with a multi-oscillator system in multicellular animals. Internal desynchronization, which has been reported in man, with various physiological functions demonstrating free-running oscillations no longer synchronized with one another, is clearly incompatible with a single oscillator model. Similarly, the fact that individual tissues can be shown to have free-running rhythms when maintained *in vitro* is also incompatible with the single oscillator system.

A third piece of evidence clearly indicating that either Model II or Model III is a better description of the circadian system has been work done in our own laboratory in which we have been able to identify some of the endocrine systems which are responsible for synchronizing peripheral oscillating cellular units. For example, by manipulating the circadian oscillations in a hormonal mediator (a,b,c, . . . , etc.) it is possible to drive a given physiological circadian function with a different period from the other functions within the organism. Our laboratory is investigating the morphology and function of the circadian timing system in primates. However, it is not appropriate here to discuss whether the circadian timing system is hierarchical or non-hierarchical, except to say that we favor Model III as the most likely organization.

Our approaches to investigating the organization of the circadian timing system have provided some new insights into the problem of circadian rhythms of drug effectiveness and toxicity in shift workers. Many separate tissues are involved in the body's response to drugs and toxicological compounds. At the risk of over simplification, these are summarized in Figure 2. It has been demonstrated that various circadian functions influence the overall effectiveness or toxicity of a pharmacological compound. For example, there may be circadian rhythms in the rate of absorption, the rate of inactivation and metabolism, the rate of



*Figure 2. Functions with demonstrated circadian rhythms which determine the overall circadian rhythms of drug effectiveness and toxicity.*

excretion, the dilutional volume of the body fluid compartment in which the drug is distributed and in the susceptibility of the target tissue at which the drug is effective.

Most studies of circadian rhythms of drug effectiveness and toxicity have been conducted in steady-state conditions where the various circadian rhythms in the functions summarized in Figure 2 presumably maintain fixed phase relationships with one another.

However, when one recognizes that the circadian timing system is a multi-oscillator system and that temporary internal desynchronization may occur after acute phase-shifts in environmental time cues, then it becomes apparent that the overall rhythm of drug effectiveness and toxicity which may have been measured in steady-state conditions is not

a reliable indication of the response that will be observed in individuals such as shift workers who are liable to show such internal desynchronization.

In summary, we are dealing with the problem where the net effect is determined by a number of functions which potentially can oscillate independently from one another. Clearly, it is necessary to learn more about the general function of the circadian timing system and the mechanisms of internal synchronization before we can set the problem of drug effectiveness and toxicity under shifting environmental conditions on a firm rational base. Work must be directed not only to understanding the steady-state conditions but also to analyzing the components which are important in determining the overall effectiveness and toxicity of a drug; and we need to learn much more about how they are synchronized with one another.

## **SOCIAL AND PSYCHOLOGICAL ADJUSTMENT TO SHIFT WORK**

*Paul E. Mott*

My assignment today is to discuss the social-behavioral consequences of various forms of shift work. But before doing that, I should like to place that discussion in a broader conceptual framework that links the worker and his family to the reality of working on shifts.

Several years ago, a number of us did a study of shift work. It was the culmination of a long series of industrial studies in which the phenomenon of shift work was an ancillary, but highly promising concern. In our major study, we interviewed or administered questionnaires to over 1,000 shift workers and over 660 of their wives. The workers were located in five geographically dispersed continuous process factories that were part of two companies.

Our analyses of the data did not show that any simple pattern of relationships between working various shift patterns and measures of health, social, and psychological well-being — self-esteem, anxiety, conflict-pressure — was related to the worker's shift.

Rotating and night shift workers reported greatest difficulty with their sleeping, eating, and bowel habits. But more serious ailments were most prevalent among the day and afternoon shift workers.

It was necessary to peel off the shift label and examine the meaning it had for the individual in terms of perceived role difficulties and complaints about body functions.

As a result of our analyses, we found a large number of variables that were factors in understanding how shift work impacted on the lives of workers and their families. They were:

- Perceived role difficulty caused by the worker's shift
- Personality factors:
  - Self-esteem
  - Anxiety
  - Conflict-pressure
- Health factors:
  - Complaints about body functions
  - General health
- Marital integration and happiness

We found, as you might expect, that perceived difficulty in performing roles was a function of the degree of imbalance between the *usual* schedule of a set of activities and the work schedule. Working on the afternoon shift, for instance, increased the difficulty of fulfilling the father role because he was absent in the evenings when the children were home.

Similarly, perceived role difficulty was strongly related to personality factors: the greater the perceived difficulty, the lower the self-esteem, the higher the anxiety and conflict-pressure. Interestingly, perceived role facilitation did not produce positive effects on these personality measures.

On a physical level, complaints about problems with time-oriented body functions were directly related to the frequency of reporting illnesses ranging from colds to rheumatoid arthritis.

These findings make sense in terms of the existing research and our commonly held expectations about the effects of shift work. Based on them, we were able to develop a plausible set of interrelated variables that appear to explain much about the impact of working shifts on people.

Yet, we were dissatisfied. By tracing the sources of our dissatisfaction, I hope to indicate some directions for future research and lay the groundwork for discussing my more specific topic for today.

One source of our dissatisfaction was "the third thing": a phase that became increasingly popular as the analysis developed. The third thing was another variable — unmeasured — that was probably influencing any given relationship we found. All of us have had experience with the third thing, but this study seemed to have more than its share of them.

We suspect that one of the key ones in the area of shift work is psychological depression: not the more situationally oriented aspect of it, but the more ingrained characterological variety. This form of depression would explain some of the reported complaints about problems with time-oriented body functions and reporting of other physical ailments.

It also could contaminate relationships between perceived role difficulties and the measures of other personality factors.

For these reasons, I suggest that measures of characterological depression should be included in studies of the human impacts of shift work in order that the effects of this variable can be parcelled out of some of the other relationships studied.

A second source of dissatisfaction was traced to the fact that the workers on any shift have behind them an assortment of histories. Day shift workers, for example, showed a higher prevalence of ulcers and general health complaints. But were these illnesses the result of working on the day shift? Or were they caused by earlier experience on other shifts? Or were their origin and onset completely unrelated to hours of

work? We were missing critical longitudinal dimensions of the problems of shift work.

Longitudinal studies are needed if we are to pin down more precisely the causes of many of the physical and psychological conditions we examined to determine the effects of working shifts. But the decision to commission longitudinal research is only the beginning of a complex methodological and conceptual series of problems. How, for example, will "date of onset" of any ailment be determined?

Another source of dissatisfaction can be traced to the near absence of hard measures for any of the variables studied. In the health area, for instance, we relied largely on self-report items. I say "largely" because at one site we checked the self-reported items against the interviewee's insurance record. We were pleasantly surprised at the accuracy of the self-reported data in general, but it would be very valuable to have more objective measures of these and other variables.

More use needs to be made of health records, including insurance claim records to study the physical effects of shift work. It might be a useful project either (1) to find factories that keep good individual shift history records and good health data, or (2) to get some factories or health insurance companies to include shift history data with the health history.

This, then, is an overview of our study and our major concerns with it. Against this backdrop, I will turn now to a discussion of the impact of working hours on social roles and relationships.

First, it is clear that different patterns of shift work *do* have selective effects on social roles. Their impact is greatest when the hours for working conflict with the *usual* times that the social role is performed.

The steady day shift is easily the one with the most advantages and the least disadvantages. Among the workers in our study who said that they would like to change their shift, virtually all of them stated a preference for the day shift. This shift has the major advantage of conforming to the "normal" rhythms of most of the worker's non-job role obligations.

The day shift workers can perform just about all of their family and social roles more easily than the workers on any other shift. They can join and participate in the activities of voluntary associations more easily, because they are free in the evening. The social disadvantages of this shift are relatively minor. Since they must get up at 6 or 7 o'clock in the morning to prepare for work, they usually cannot stay up late in the evening. Commercial activities, such as shopping and banking, are generally restricted to their days off or those evenings when the business establishments stay open. Also, while it is not impossible to maintain a second job when working the day shift, it is less easy than it is for the

afternoon and night shift workers. The latter can take one of the more plentiful daytime jobs.

Socially, the afternoon shift is the most disadvantageous of all of the shifts, particularly for the younger, better educated worker with small children living at home. Except for his days off, the afternoon shift worker seldom sees his school-age children; they are home while he is working and at school when he is at home. All activity associated with the evening hours, whether it is simply being at home with his wife and being a companion to her or going out socially with her or alone to see friends, is possible only on days off.

The advantages of the afternoon shift for the social life of the worker are few, but many workers value them highly. Some of these workers look forward to the hours after 11 p.m. when the children are in bed and they can sit and visit with their wives for awhile, perhaps while watching the late show on television. Others enjoy going out after work with their friends who are on the same shift. This shift also makes it easier to attend to business activities and to take a second job.

The wives of afternoon shift workers tend to find it a little easier than the wives of workers on the other shifts to perform their functions as mothers. This subject should be investigated more closely. It may be that the wife enjoys the freedom she has to make decisions about the children, her increased freedom resulting from her husband's absence from the home after 3 or 4 o'clock in the afternoon.

Our findings about the night shift did not match our preconceptions. We had expected that this shift would cause more problems for the workers than the data showed. This shift does not interfere with family and social roles nearly as much as the afternoon and rotating shifts do. The night shift workers have the greatest difficulty in their role behaviors as sexual partners and protectors for their wives. Their absence from the home during the late evening hours is responsible for these problems. The night shift worker, like the day worker, must leave social events fairly early, but in order to get to work and not to go to bed. Like the afternoon shift, this shift facilitates the holding of a second job and attending to commercial affairs.

The weekly rotating shift clearly provides the most problems for the workers and most of these problems derive from the simple fact that the workers change their shift each week. Because they regularly spend a week on each of the other shifts, they experience all of the advantages and disadvantages of those shifts. When they are on the day shift, they can lead a life that conforms to the normal rhythms of our society. But when they are on the afternoon shift, they experience the difficulties with their family and social roles that the steady afternoon shift workers experience. For the rotating workers there is an added difficulty; their

friends have difficulty keeping track of their shift changes. For this reason, the rotator is often left out of social activities.

These are some of the ways that the *timing* of work interferes with or facilitates the social roles of shift workers. But the variables we studied were highly interactive. For example, problems of adjusting time-oriented body functions will affect the social lives of workers. If they are tired, they are probably not going to feel like being socially active.

These are some of the things that we have learned. But like so much research, it raises more questions than it answers. I should like to end with a few observations and some ideas for research on the social impacts of shift work.

Back to the third thing: As our research progressed, we became increasingly aware of the importance of the attitudes of other members of the worker's family and how they relate to his ability to cope with his shift. Much of the difficulty in coping with shift problems was transferred, voluntarily or otherwise, to their wives and children.

Wives often adjust their schedules to make things easier for their husbands. They do the noisier chores when their husbands are at work or awake. They adjust their own sleeping schedules, keep their children quiet when their husbands are sleeping, and, in the case of rotating shifts, try to hold their social lives and friendships together despite the vicissitudes of that schedule.

Marital happiness may be a key ingredient in the family's ability to cope. One of the hallmarks of a happy marriage is the more open give-and-take — the role flexibility — between husbands and wives.

In these fortunate families, when there are problems to be solved, the solutions are less likely to be constrained by the rigidities of role definitions found in less happy marriages.

Shift work presents problems; I believe that they probably are more likely to be solved in happy marriages than unhappy ones. But these conjectures need to be studied. And beyond them, we need better information on the effects of the solutions on the wives and children.

I have mentioned some of the ways that different shift schedules affect non-work activities. But there are whole areas of work/non-work activities that have not received adequate attention. Workers often try to select those shifts that facilitate their other interests. But in addition to leisure, these interests include taking second jobs, caring for the children while their wives work, or avoiding the major problems in their lives.

These strategies argue for having several different types of shift patterns in the same factory and community, if there is an interest in accommodating to individual and family goals.

The use of a single rotating pattern, for example, frustrates them. Therefore, in addition to studying how different shift patterns affect people,

we need to consider the desirable *mixes* of patterns that help people to achieve their goals. There will be some resistance to this set of concerns on the part of plant managers who understandably would prefer the simplicities of a single shift pattern, but the concerns are socially important nonetheless.

Turning to the more traditional focus on work and leisure: I have formed the impression that many workers are willing to tolerate some seemingly difficult shifts if the trade-off is larger block of free time. We found workers who were willing to put up with the problems of weekly rotation in exchange for the block of four days off that occurred once each month.

I wonder what workers would do if they could design their own shift patterns? The evidence available to me indicates that many would opt for patterns that gave them large blocks of leisure time. In one factory where the workers were involved in the design of shift patterns, they elected to work virtually every day for 13 weeks in exchange for 10 consecutive days off during that quarter. We need to examine these "large leisure block" patterns with more care. What are the perceived benefits? What are the costs to the family and to the psychological and physical well-being of the worker?

On a related note: we should encourage more worker participation in the design of their shift patterns. But we ought to make them aware of what the consequences are likely to be of their choices.

Finally, we need to consider the whole phenomenon of flextime in relation to shift work. Can flexible schedules be developed that would meet the requirements of labor-efficient production *and* the non-work goals and needs of workers? The values of flextime are obvious; the difficulties of applying it to continuous process industries are equally obvious, but, as a believer in human ingenuity, I think they can be overcome and are worth overcoming.

## **SOCIAL AND PSYCHOLOGICAL ADJUSTMENT TO SHIFT WORK: DISCUSSION I**

*Don Tasto*

I should like to do three things during this discussion. The first is to summarize some general statements from some of the conclusions about psychological, social, attitudinal and emotional impacts that shift work has upon the worker. Second is to point out some design problems and present to you a model which may help overcome some of the design problems that have led to equivocal conclusions in these regards. Thirdly, something I hadn't planned, but since it seemed to be relevant because of the sleep problems encountered in this regard, we have been doing some research on people with sleep problems so I might mention briefly the non-pharmacological approaches that we are doing in that regard.

In regard to attitudes of shift workers, although shift work has been described by Bands as "resignation" rather than adaptation and by Downing as acceptance rather than acclaim, the result of attitude research on shift workers has not produced unequivocal results. Foolsh, Bass, Mann and Hoffman, as well as the Phillips Company Study, have all shown predominantly negative attitudes toward shift work.

By contrast, Blackelock, Taylor and others have found greater percentages of people liking shift work. A more refined analysis of attitudinal trends suggests, as Martadahl has pointed out, that positive attitudes toward shift work are directly related to the length of time on the job and inversely related to education and skill level.

In regard to emotional outlets, the work of Ulich and that of Smith, Melton and McKenzie has shown such factors as increased irritability, nervousness, bad temper, fatigue, sleeplessness and a less positive affective state to be attributed by workers to shift work.

In regard to family relationships, referring to the work of Ulich and that of Bass, we can infer what seem to be the major problems in the shift worker's relationships with wife and children: the absence of the worker from the home in the evening, problems in sexual relations, and difficulties encountered by the wife in carrying out her household duties. In addition to the work of Hoffman and Bass as well as Deilamar and Walker, job satisfaction as reported by the worker appears to be related

to the perception of shift work that is held by other members of the family. If other members of the family perceive the shift work to be a positive thing, that perception is usually held by the worker himself. If the family sees shift work as something negative, then the worker himself tends to have that perception.

In regard to some social factors, the research, particularly that of Blackelock, Mann, and Hoffman, indicates that shift workers participate less in organizations, attend fewer meetings and are not likely to hold offices. Frequency of social contact, however, varies considerably as a function of the organization. Mott suggests that some of these variations in social contact are attributable to differences in communities. Perhaps social contacts are easily established and maintained in smaller communities that are predominantly comprised of shift workers in contrast to larger communities where shift workers are sparsely located throughout the city.

Now differences in studies have arisen and conclusions, particularly in regard to sociological and psychological factors, do not always seem to be consistent from study to study. What I would like to do is to propose that, in part, the reason for this has been that some variables either have not been controlled or accounted for.

We start with a basic contingency table in which we have a type of worker (and by type here we will refer to recent or long term shift worker) by shift schedule. I think it is important that we know this information in doing a study because, in the past, people have gone into an institution and have looked at workers and have said: "You are a shift worker, therefore you fall into the category of a shift worker" without taking into account the history of the worker. Are they recently created shift workers, or have they been shift workers for a long time? The other problem that you run into is the people who are considered to be non-shift workers in some studies may have been shift workers and recently have become non-shift workers; and one reason they may have become non-shift workers is that they weren't adapting very well to shift work. Because of these problems inherent with self selection factors at work, it becomes critical that we keep information on these factors.

If you can look at these four along one side and then take a look at the type of shift — day, evening, night and rotating — you'd end up with a four by four contingency table and you're not going to have all these cells filled.

You are not going to have non-shift workers who are working the evening shift. By and large, the three major ones to consider are your recent long term day shift and your evening, night and rotating shift workers. The information on your non-shift workers and the information

on your day shift workers can be used as controlled data. Supposing we added another variable and that is the variable of different types of industries. We can superimpose different types of industry upon this contingency table here and end up with whatever number of industries were studied in a given study by these which will give us more cells than we will want to fill in any given study.

Now what if, in addition to these variables, we are going to be studying workers' attitudes about shift work and we suspect that such factors as extraversion and introversion, IQ, individual family size, number of hours working other jobs, age, etc. may be related to a person's attitude about shift work. We may suspect that is true and somebody might become rather boggled about the fact that you have to control for all of those variables. In a study that we are proposing right now, somebody will say: "Well, what about those workers working other jobs; maybe we should eliminate them from the study." And somebody else will say: "There's an awful lot of people who work other jobs; we can't really eliminate them. If we eliminate people from the study based on all these different kinds of variables, we are going to end up with nobody and it's going to be very costly."

The way to get around this is not to eliminate anybody from the study because of any of these variables, but rather what we need to do is to account for them. We need to keep measures on people. If we thought these were important, we can keep measures of intraversion and extraversion; we can get intelligence measures; we can get family size; we can get number of hours on other jobs; and so on. Then we can relate these variables to our outcome measures and we can do it by cutting through this category anyway we want to.

If we are dealing with oil refineries, for example, we can cut apart from whatever shift anybody is working and apart from the type of shift they are working. We can correlate any given variable with attitude. We can break it down by looking at just recent shift workers across all industries. We can look at recent shift workers who just happen to be working rotating shifts, etc., etc.

In conclusion, with regard to design, I think it is important to keep in mind — at least in the practical world of trying to study people — that it is not so important to eliminate people from a design because of factors that are related but rather to keep information on people and to at least have history on these people in terms of their shift work.

Ulcers seem to be related to shift work. Mott did not find a significant relationship in his study but then began to wonder whether it was not possible that a lot of day workers with ulcers developed them on previous shift schedules.

These are some of the design considerations in getting around the variables of selection within an institution.

## **SOCIAL AND PSYCHOLOGICAL ADJUSTMENT TO SHIFT WORK: DISCUSSION II**

*Wilse B. Webb*

We continue today to follow a truism of interdisciplinary meetings; each person at such meetings tends to view the world through his own interests and research background. I find myself involved in a happy accident. My present research interest — sleep — certainly relates to shift work and an earlier interest — accident research — holds some promise of an approach to the shift work problems of sleep.

Let me first display in a simple way the complex relationships between shift work and the sleep process. In Table I, I have assumed that an individual is working from 8 a.m. to 4 p.m. (W), is off from 4 p.m. to 12 m. (O) and sleeps from 12 m. to 8 a.m. (S). Let us now have him work from 12 m. to 8 a.m. and be off from 8 a.m. to 4 p.m. and sleep from 4 p.m. to 12 m. A, B, and C give three possible schedules. In the three schedules, I have kept the total amount of sleep and waking constant in shifting to the night shift over three days.

You can see that the varying possibilities (of a few selected) are remarkably different. In the A schedule, the person is awake for two 24-hour periods. In the B schedule, the person is awake for a 32-hour period. In the C schedule, the sleep is broken into two four-hour periods. By varying the amount of sleep and waking within these time periods and the placement of sleep, the patterns are almost infinite. In the patterns displayed, I believe we could certainly expect some consequences of deficiency from a 32-hour period of continuous wakefulness.

Whatever the pattern of sleep, however, sleep research is progressing to the level that we can begin to make sound predictions about the response of the sleep process to varying regimens of sleep/wake patterns within a 24-hour schema. In short, we are beginning to know the "laws" of sleep. I am making the brash statement that, if you can cite the temporal patterns of sleep and waking, we can begin to tell you, with considerable accuracy, about the subsequent sleep, its ease of onset, and sleep after onset.

Let me give you a few remarkable examples. Figure 1 presents the laboratory-determined relations between the amount of prior wakefulness

TABLE I

*The possible shift schedule with equalized sleep-waking ratios.*

|           | A    |    |     |                          |
|-----------|------|----|-----|--------------------------|
|           | I    | II | III |                          |
| 12 M-8 AM | S    | W  | W   | 2 — 24-hour wake periods |
| 8 AM-4 PM | W    | S  | O   | 3 — 8-hour sleep periods |
| 4 PM-12 M | O    | O  | S   |                          |
|           | B    |    |     |                          |
|           | I    | II | III |                          |
| 12 M-8 AM | S    | S  | W   | 1 — 32-hour wake period  |
| 8 AM-4 PM | W    | W  | O   | 1 — 16-hour wake period  |
| 4 PM-12 M | O    | O  | S   | 3 — 8-hour sleep periods |
|           | C    |    |     |                          |
|           | I    | II | III |                          |
| 12 M-8 AM | S(4) | W  | W   | 3 — 16-hour wake periods |
| 8 AM-4 PM | W    | O  | O   | 2 — 4-hour sleep periods |
| 4 PM-12 M | S(4) | S  | S   | 2 — 8-hour sleep periods |

S = Sleep  
W = Work  
O = "Offtime"

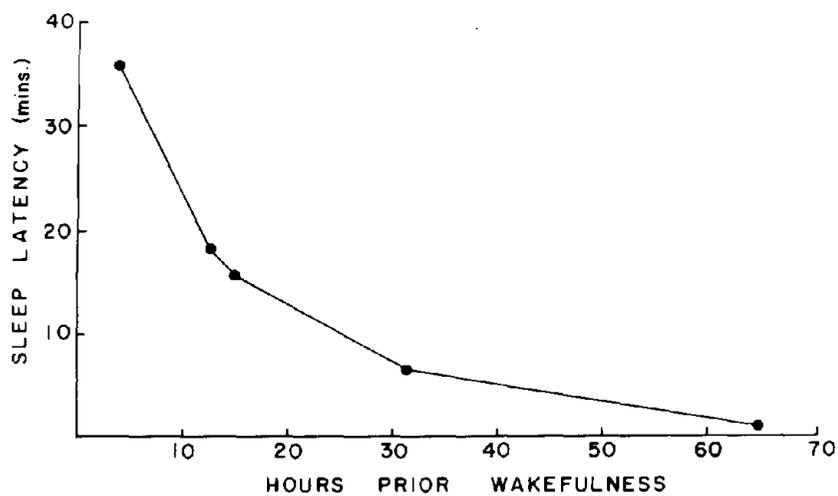


Figure 1. Prior wakefulness and latency

and the latency of sleep. Figure 2 presents the relationship between prior wakefulness and deep sleep after sleep onset. From Figure 3, you can infer what effects on the structure of sleep follow reducing the length of sleep. For example, if you reduce sleep by one-fourth you have little effect on Stage 4 (dcep) sleep but you reduce the amount of REM (dream) sleep by considerably more than 25%. There are strong effects on sleep relative to when sleep begins. Figure 4 shows the differences in latency (length of time to get to sleep) dependent upon when sleep begins. In this instance, the amount of prior wakefulness is held constant. There are similar strong effects on the substructure of sleep and the tendency to wake up in terms of the circadian onset time.

The point that I am making is that sleep is quite lawful in its responsiveness to variations in time, and time variations are inevitable in shift work variations in prior wakefulness, sleep length, and sleep onset time. We approach the point where, if you will specify the sleep/waking schedule for a group of workers, we can make solid projections about the nature of their sleep.

But all of us know that shift workers do not necessarily follow neat schedules, are widely different in their personal strengths and weaknesses, and sleep in widely varied physical and social environments. All these may influence the sleep of the particular shift worker.

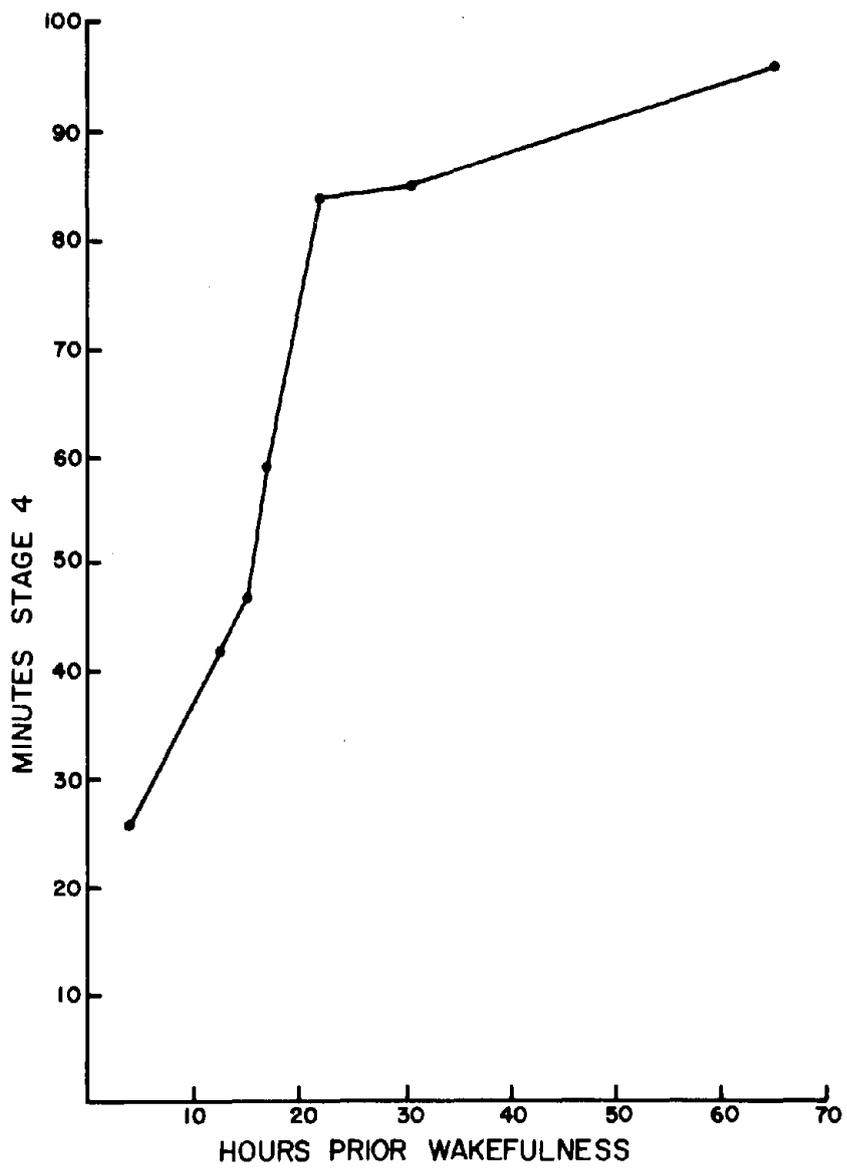
In an over-simplified schema, at least the following factors may be associated with good or bad sleep in a shift work setting.

- Sleep factors (prior wakefulness, etc.)
- Health factors (young or old, sick or well, etc.)
- Psychological factors (anxiety, needs, achievements, etc.)
- Environmental factors (physical and social surroundings)

These factors interact and are different in their weighting. In some individuals all these things may be on the good side: a regular sleep patterning, good health, sound personality and a supportive environment. In others, there may be trouble in one, two or all of these dimensions.

Who then will be able to “hack” shift work in terms of sleep? It will not be predictable from the schedules of sleep alone if we are to speak of an individual. It obviously will depend upon a complex interaction of all four of these generalized factors.

How, then, are we to approach the question of shift work regarding the individual? I think we may approach it in the multi-faceted way that we approach the reduction of accidents: selection, training, and environmental control. I believe a similar approach to sleep and shift work will be necessary. There will be some individuals, primarily on “Health” and “Psychological” grounds, who should not go on shift work and should be “selected out.” There will be many factors in terms of “Sleep” routines and “Environments” that individuals must be “trained” to avoid or mini-



*Figure 2. Prior wakefulness and stage 4*

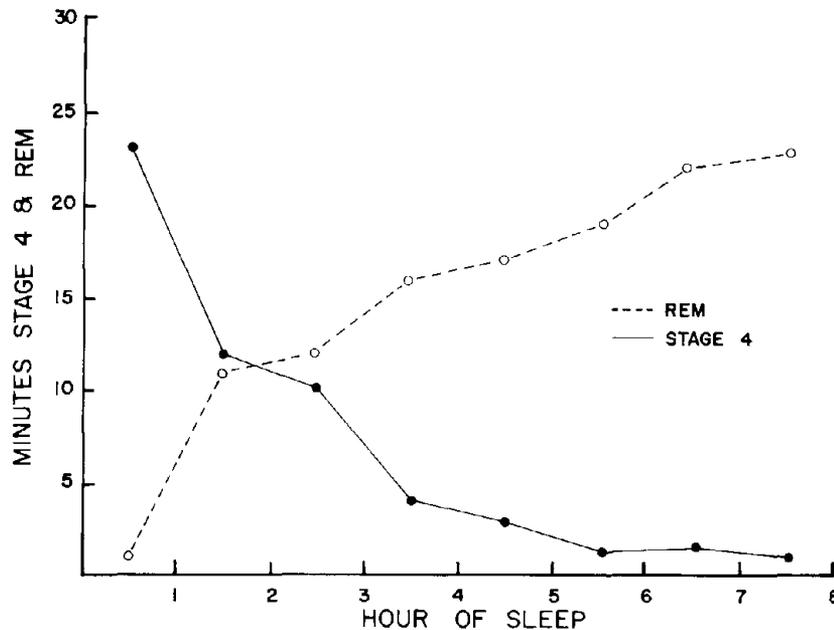


Figure 3. Length of sleep and stages of sleep

mize. We will have to work on “Environmental Controls” through arrangements of shift schedules, within shift routines, subsidies of sleep improved environments, concerns with family relations, etc.

Specifically, we need better individual “screening” tools, more educational materials to provide industry, unions and workers themselves and more systematic controls of the worker environment if we are to avoid or, at least, minimize sleep problems.

One last set of comments about the relevance of sleep as a shift work “problem.” Every survey of shift work that I know of has turned “poor sleep” up as one of the most prominent complaints. But are “complaints” sufficiently important to be concerned about? In this instance I believe so.

At the simplest level, common sense tells you that a person who is sleeping poorly is simply not at his best. Secondly, the person is likely to try to do something about it and in this instance he is likely to start taking sleeping pills. And this is a well documented disaster route. Most critically, this is a fundamental biorhythm that is built into the very fabric of human existence. While temporary and even acute variations may be tolerable, I do not believe that a chronic disturbance can possibly be without cost and we are moving into a world where shift work is becoming

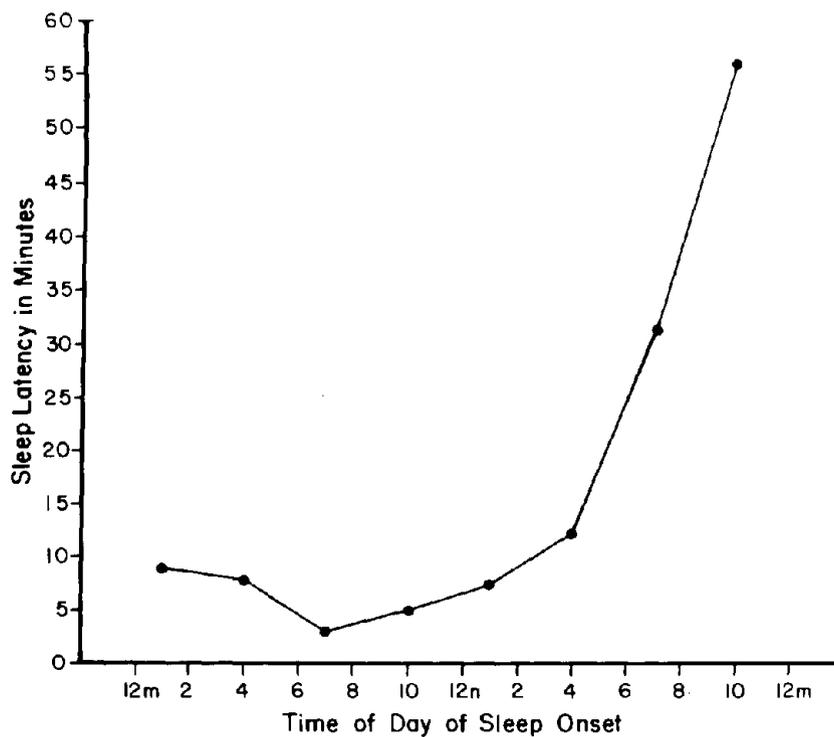


Figure 4. Sleep onset time and latency of sleep

a constant and chronic aspect of workers. Yes, even beyond “morale” and “motivation” factors, I am convinced that sleep is a practical element in shift work concerns.

## ACCIDENTS, INJURIES AND SHIFT WORK

*W. P. Colquhoun*

I'll start with in anecdote; (I should like to say it was a humorous one, but, I'm sorry, it's a tragic one). Shortly before I left England, there was a very serious railway accident in which a train driver went through a section restricted to 20 MPH at high speed. This was the third successive day he had been through this section so that you couldn't say he didn't know it was there, and he went through at a speed eyewitnesses are putting at at least 70 MPH. This is all "sub judice" and an inquiry will have to decide what the true causes were. However, the thing that immediately struck me was that this accident occurred at 2 a.m. and that this driver had been on night shift for three successive nights.

In the inquiry, these things no doubt will be mentioned, but I think it's very depressing, and shows our state of lack of knowledge at the moment, that nobody is going to be able to say at the inquiry just how much, if any, effect these particular facts had on the accident. Was it totally irrelevant that it was 2 A.M. and that the driver had been on night shifts, or not? We just don't know. Anyway, a particular case like that could be matched up with many similar accidents which happen in the daytime.

At first sight, then, we have a non-problem in respect to accidents because, as far as I can see, there is general agreement that there is no apparent relationship between accident rate and time of shift. That is to say, there are no more accidents at night than there are during the day. In fact, most studies suggest that there are actually fewer accidents at night than there are during the day. But factory conditions during the night are often different; in fact, I would say probably *always* different from those during the day. So it's just not possible to make valid comparisons. That's point one that I'd like to make: *conditions are rarely, if ever, the same by day and by night*, so actual accident figures can be very misleading.

The second point concerns the number of reports of accidents and injuries that people bother to make. I gather from what I've been reading that maybe only something like 60 to 70% of actual injuries are ever reported. At any rate, the reported accidents are often not very numer-

ous, so that in any particular factory we simply don't have enough data for comparison of different shifts. However, *possible* accidents — accidents that didn't actually happen ("near misses" as they say in the flying fraternity) or "critical incidents" if you like — may be much more numerous on certain shifts, but we don't know. They're often not reported at all. There's no incentive to report them (except in the flying community, where I gather there is). But even if they are reported, they're rarely reported in sufficient detail or at the actual time of occurrence. It may be several hours later or the next day before the near-accident is reported, by which time the person involved perhaps has forgotten some significant details about it.

It could well be that these critical incidents — possible accident situations — are, in fact, quite frequent. We do not know. The point I want to make is that, even though an actual accident may be a rare event in any particular factory or plant, in more and more cases nowadays, such an accident could be disastrous.

I don't mean to be callous, but if you lose a finger by cutting it through making some slight error in your manual task it's very unfortunate for you, naturally, but it's just you, it's just your finger.

But think of a chemical plant. We had a serious accident — this time in just such a plant — a few weeks ago in Britain which destroyed an entire community, quite apart from killing a large number of people. That's a chemical plant. Now think of a nuclear power station. We all know what might happen. Most of the time we don't want to think about it. What I'm saying is that any rise in the probability or possibility of an accident at any particular time of day or on a particular shift is, I think, extremely important even though the accident hasn't yet occurred. It's going to sooner or later. Any information we can get on this probability is important and is going to be increasingly so in the future.

I would argue that, since human error is accepted to be a factor in some 80 to 90% of all accidents, the only way to look at this thing is to study the circadian variation in factors like alertness, speed of response, and the likelihood of making "mistakes." This already has been mentioned this morning by Professor Halberg and Dr. Hayes, and I, too, think we've got to look at this first *in the laboratory* where we know that the conditions are the same (or as near as we can make them the same) at different times of day and night. We must consider work periods of different lengths also. In this way, we can see whether these mental functions do, in fact, show circadian rhythms like nearly all physiological processes do (we've seen plenty of examples this morning of the latter), and how these rhythms are affected by fatigue. Well, this is what we and many other people have been doing.

I'm going to suggest here that the results that we and others get may well indicate the expected variation in what I will call "accident causation probability" or, if you like, "accident causation potentiality." Now, we know that all accidents have multiple causes, but given that they all come together, then if we study what I'm trying to describe, the results we get will give us some indication of the probability that an accident will occur given these other conditions.

Perhaps I could mention some results of some of my European colleagues. Some of these have been referred to by Dr. Levine this morning. The top graph in Figure 1 is just a simple laboratory study of reaction time. There are many such studies, including one that we've done, that show much the same thing. We know for sure, then, that there is circadian variation in reaction time, in the laboratory. The second graph is the classic Swedish study, derived from data collected for something like 30 years on real shift workers doing a real job reading gas meters. The graph shows the hourly rate of reading errors on these

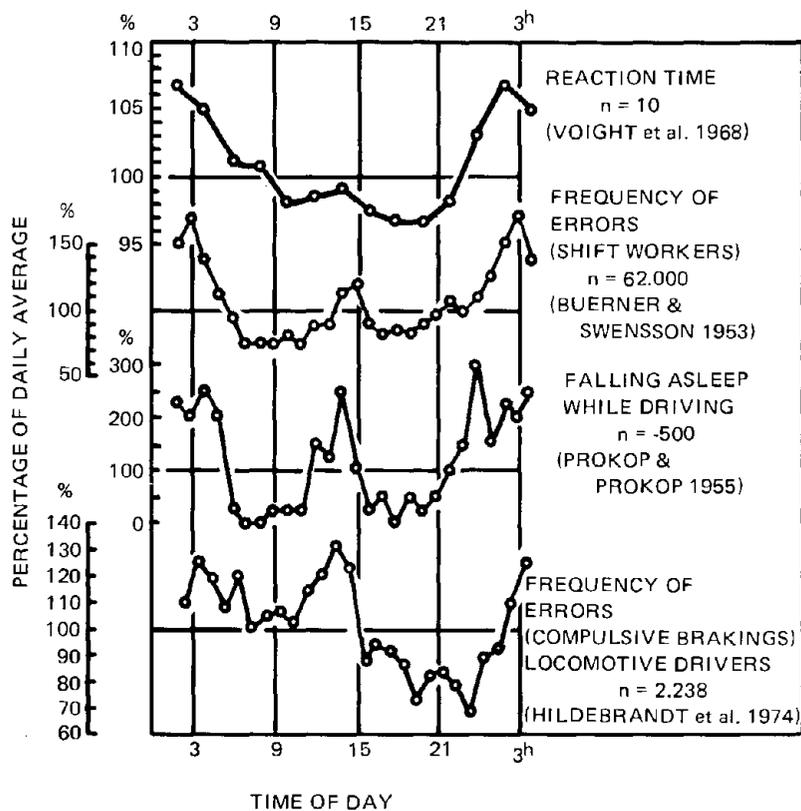


Figure 1. Circadian variations in different functions.

gas meters and it shows a clear circadian periodicity reaching its maximum during the night shift.

The next graph (also mentioned this morning by Dr. Levine) alarms me considerably because the probability of falling asleep while driving a car apparently is as high in the middle of the day as it is in the middle of the night. This car-driving data perhaps demonstrates the possibility of an accident which luckily didn't occur. The bottom graph (which comes from a study also mentioned this morning) represents results from German train-drivers whose trains come to an automatic stop if the driver fails to respond to a repeated signal in the cab. Again, you've got a clear 24-hour pattern in the relative frequency of such brakings.

Any of the results of these field studies could have been influenced by other factors. Since I didn't do any of the studies I'm not sure. However, even though I don't know the details, I suspect that perhaps the gas meter reading study is least likely to have been affected by other factors because as far as I can make out the job there was exactly the same on any shift. However, although the others might have been so affected, they all suggest (particularly the Swedish study) that accident probability should be higher on night shifts than on day shifts — *should* be, but isn't according to the actual accident figures.

Perhaps we could turn to the controlled studies done in our own laboratory. The Navy has been the main supporter of this research, mainly I suppose because at sea people always have had to work around the clock since a ship doesn't usually stop at night, and also because a mistake at sea obviously can be disastrous. You can run aground, you can hit another ship and so on. The United States Navy asked Professor Kleitman some time ago to look at this problem, and probably his best known result is shown in Figure 2. These United States sailors were working a very rapidly rotating shift system with four-hour duty spells in which the cycle length was only four days, but Kleitman was able to show (I think convincingly) that the speed of performing a color naming test was correlated with the body temperature attained during the different duty periods. Although Kleitman's results were all known some time ago, the British Navy asked us to look at the same problem arguing that British sailors are not the same as American sailors. So, we started all over again and looked at essentially the same situation to start with, i.e., a very rapidly rotating system which, in the British Navy, is only three days, not four, but which otherwise is very similar indeed.

Figure 3 shows that we found the same sort of thing as Kleitman, namely, that performance depended on the time of day at which the four-hour watch was held and that efficiency was related pretty closely to body temperature. The results were not quite as good as Professor Kleitman's but still I think they are pretty good. You can see in the left-hand

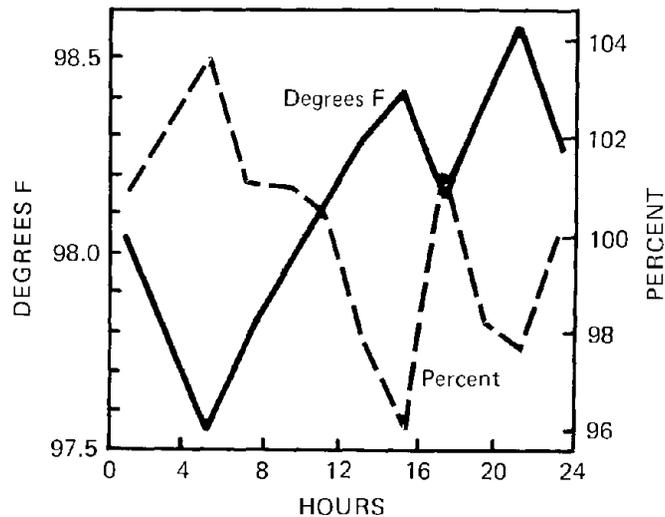


Figure 2. Variations in oral temperature and relative variations in color-naming time, in different watches of a rapidly rotating U.S. Navy shift work system.

graph (which was our main interest since there we were trying to simulate a sonar operator's job) we have a reasonably close correlation between the probability of detecting a very faint auditory or visual signal and the temperature at the time of day at which the watch is held. So in alertness, and also in speed (middle graph, which shows how fast you respond to a signal when you do detect it), we have clear evidence of circadian variation under simulated shift-work conditions. (The right-hand graph also is an indication of speed, although it's an indirect measure. It's how fast you work at a very routine, boring job of adding up endless short columns of numbers.)

Thus, in alertness and speed at least (and probably also in "mistake probability"), there does seem to be a clear indication that what I'm terming accident causation potentiality varies circadianly, and that this potentiality is higher on the night shift than on the morning shift, and lowest on the afternoon-evening shift. This, if you like, is the order in which the laboratory results predict the accident probability.

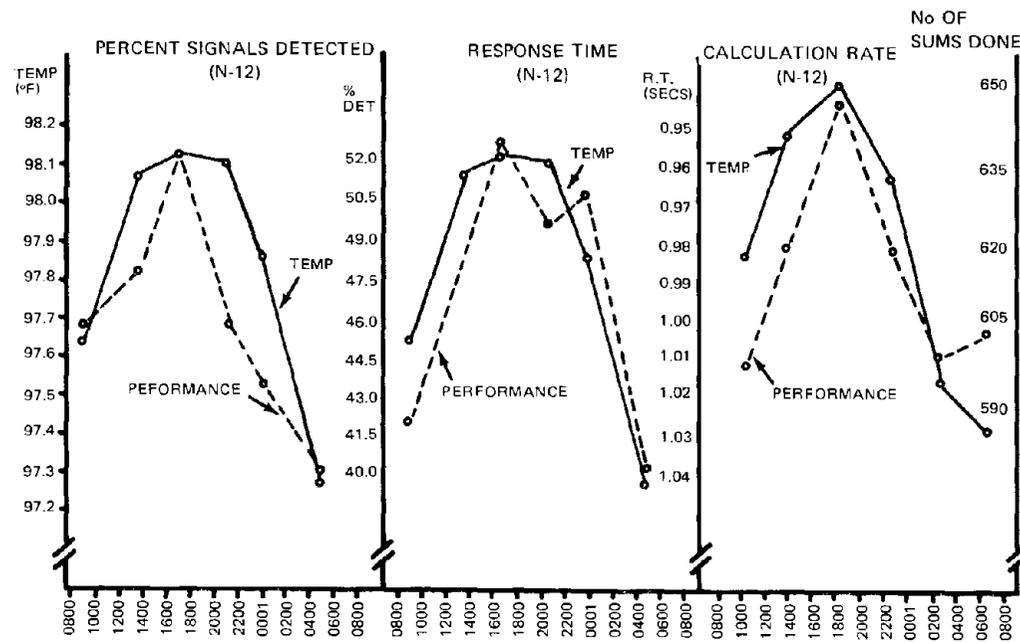


Figure 3. Variations in oral temperature, and in three performance measures, in different watches of a rapidly rotating British Navy shift work system.

We then departed from the terms of our original contract and increased the length of the duty spell (which traditionally is four hours) to eight hours, to make things comparable to the industrial situation, because we were concerned that this work should be generalizable to more than just ships. We looked first at 12 consecutive day shifts — just ordinary day work, but with no “weekend break” — and found the same thing as we did when we were looking at simple “time of day effects.” By “time of day effects” I mean results from experiments in the laboratory where we test people at intervals during the day for very short periods and they do nothing for the rest of the day. In these laboratory studies, we already had found increases in efficiency throughout the day which approximately paralleled body temperature changes. Figure 4 shows the results of six such experiments carried out by my colleague the late Michael Blake, all conducted during normal hours of the day, with the subject having had a normal sleep. Each one showed a very similar pattern of performance (note that all measures, except signal detection rate, are of *speed*; no measure of *accuracy* in Blake’s experiments showed any variation whatsoever). There is a rise during the morning before noon, then a slump — the “post-lunch dip.” In each case there is, then, a recovery and performance reaches a maximum at nine o’clock at night, the last time of measurement in these experiments.

I said that when we did our simulated shift work studies and took day work only over 12 consecutive days we got just the same thing. Figure 5 shows this, in terms of signal detection rate in a vigilance task (this has been averaged over all 12 days as the trend was similar each day). The shift was from 8 a.m. until 4 p.m. (during which body temperature was rising, of course, as part of the normal rhythm) and again, performance at this detection task rose rapidly in the morning and then ceased to rise, which (referring to Figure 4) presumably represents the post-lunch dip. (In fact, I know it does because in later experiments we extended the length of the shift to 12 hours, and performance rose again to reach its maximum at 8 p.m.) So we get the same results in an eight-hour, even a 12-hour, “laboratory shift” as we get when we’re doing a straight “time of day” laboratory experiment. This also holds for speed of response (see Figure 6).

Next we turned to night shifts from 10 p.m. to 6 a.m. (the standard industrial night shift), and Figure 7 shows what happened to the temperature rhythm over the 12 consecutive nights of the experiment. You can see that on the sixth night the rhythm has changed; it has partly flattened. But on the final (12th) night of the experiment, it has flattened almost entirely so that there really isn’t any rhythm there at all. What has *not* happened is a phase-shift in the temperature rhythm to coincide with the change in the sleep-waking pattern. The rhythm has just disappeared.

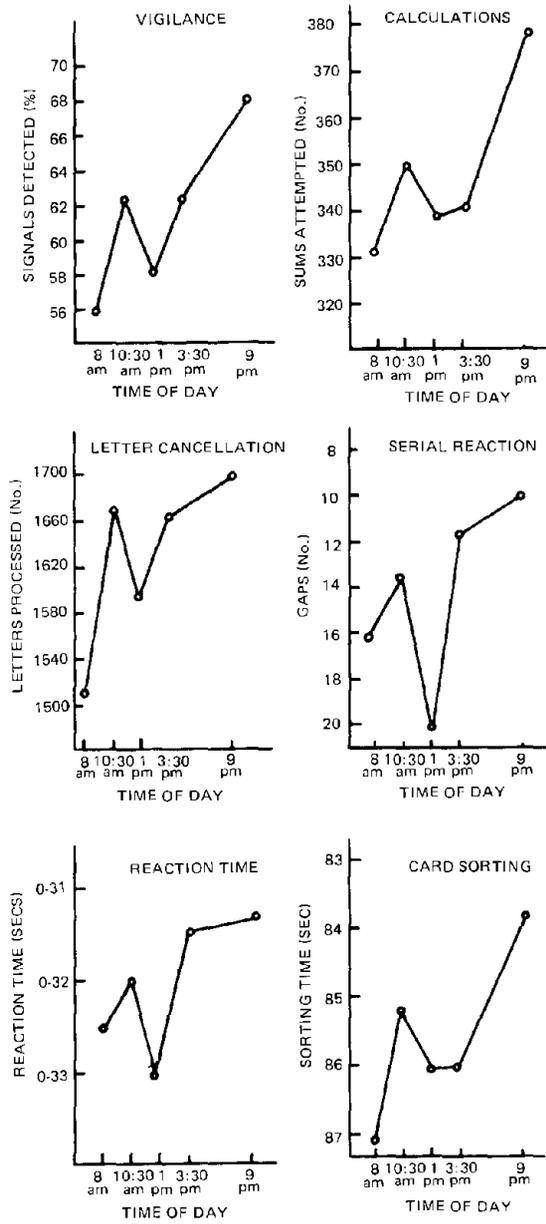


Figure 4. "Time of day" effects in six different performance measures.

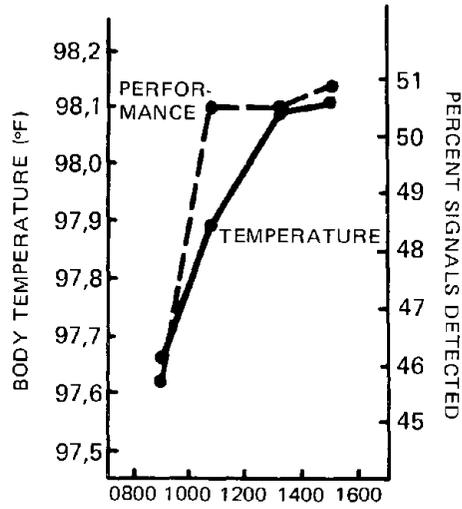


Figure 5. Changes in temperature, and in signal-detection rate in a vigilance task, during an 8-hour shift.

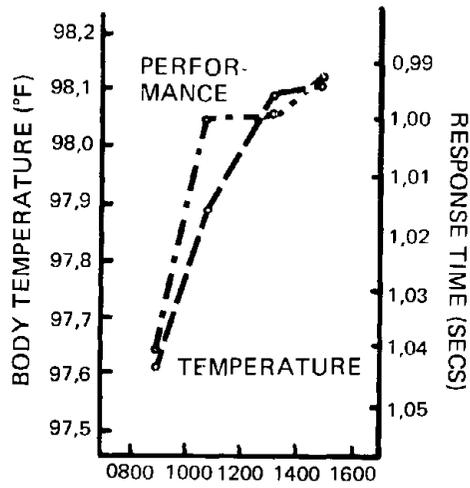


Figure 6. Changes in temperature, and in response-time to detected signals in a vigilance task, during an 8-hour day shift.

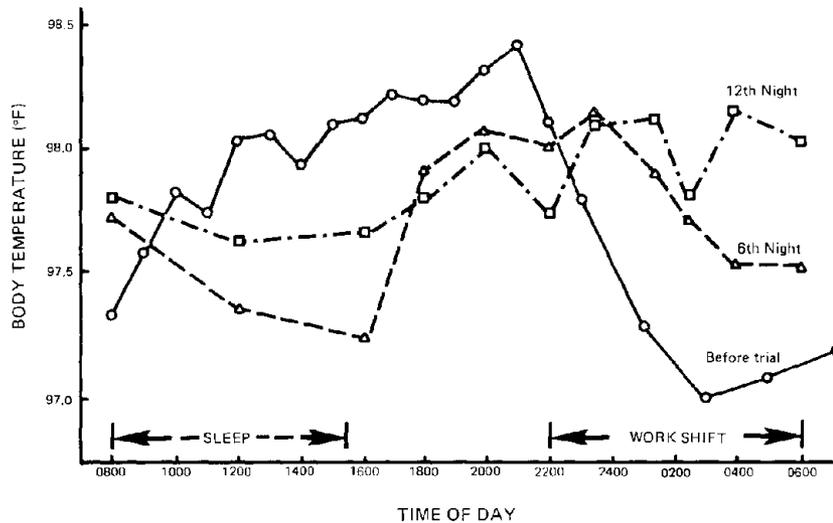


Figure 7. Changes in the circadian rhythm of body-temperature over a 12-day period of consecutive night shifts.

We had to stop the experiment there; I'd like to know what would have happened if we'd been able to go on, but neither the subjects nor we could have stood it one day longer!

Now in predicting the relationship between temperature and performance which we'd already observed, we expected, during the 12-day period, that performance at the tasks we were using (the detection task and the calculations task) would fall quite dramatically during the shift at the beginning of the period and less so as the experiment went on until by the end of the 12-day period there would probably be no decline at all. Figure 8 shows in a very summarized form what we actually got for the detection-rate score, taking the first six consecutive night shifts together and then the second six night shifts together. You can see that during the first six days the temperature was falling during the shift, and in the second six it was falling less. Performance in the first six nights was tending to follow the decline in temperature, as we'd expected. During the second six nights this fall had disappeared, though the trend was now somewhat erratic.

Figure 9 shows the other measure, response time, which again showed a fall-off in the first six nights, and then perhaps a less marked fall-off during the second six nights, indicating a certain tendency for reaction time to follow the changing temperature also.

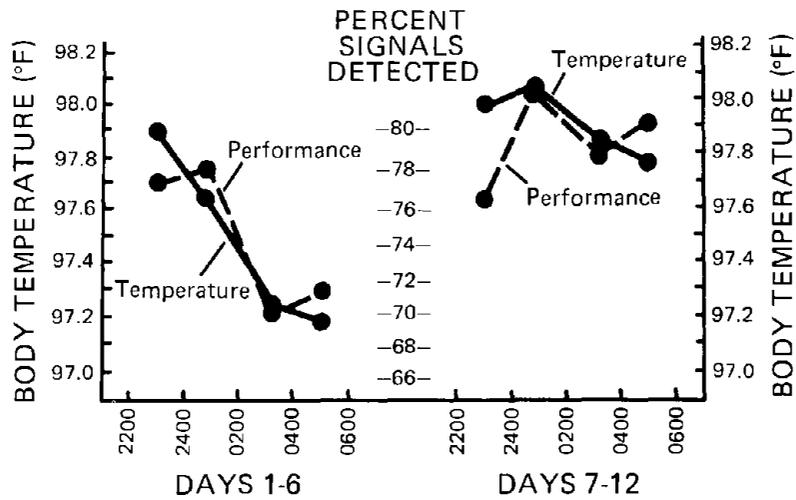


Figure 8. On-shift trends in temperature, and in signal-detection rate in a vigilance task, for the first and second six-day periods of a 12-day night shift experiment.

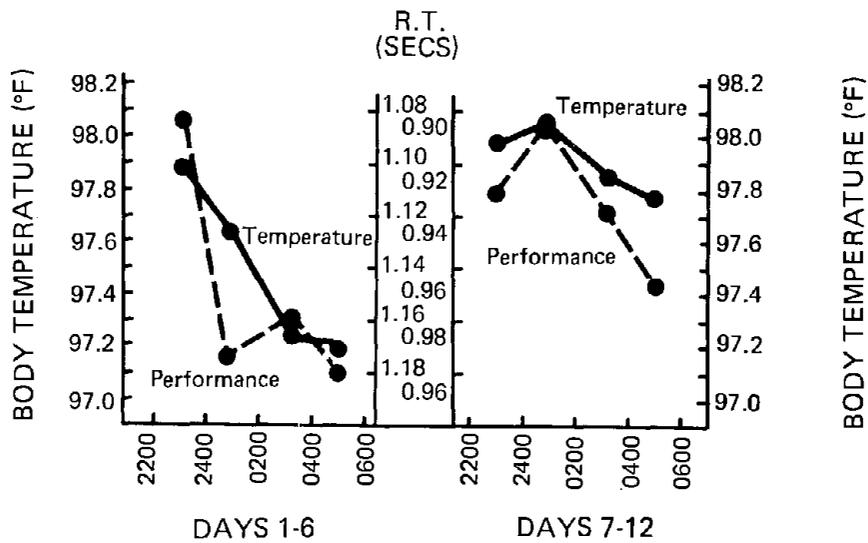


Figure 9. On-shift trends in temperature, and in response-time to detected signals in a vigilance task, for the first and second six-day of a 12-day night shift experiment.

Figure 10 shows the changes on a day-by-day basis (expressed as three-day running averages to smooth the curves). The top graph shows the temperature trend during the night shift period from 2200 to 0600; and, as you would expect from Figure 7, this gradually is showing the adaptation towards the flat line we saw there.

On the second graph, you have the trend in the response time measure, which is showing, I suggest, a change very similar to the change in the temperature trend. Now switch to the bottom graph; here you have the rate at which people worked in the extremely boring task of adding up sums. This is another sort of speed measure and again I suggest that this shows a change in trend similar to the change in temperature trend. However, looking at the graph which was our main interest — the detection rate in the simulated sonar task — though I don't know whether

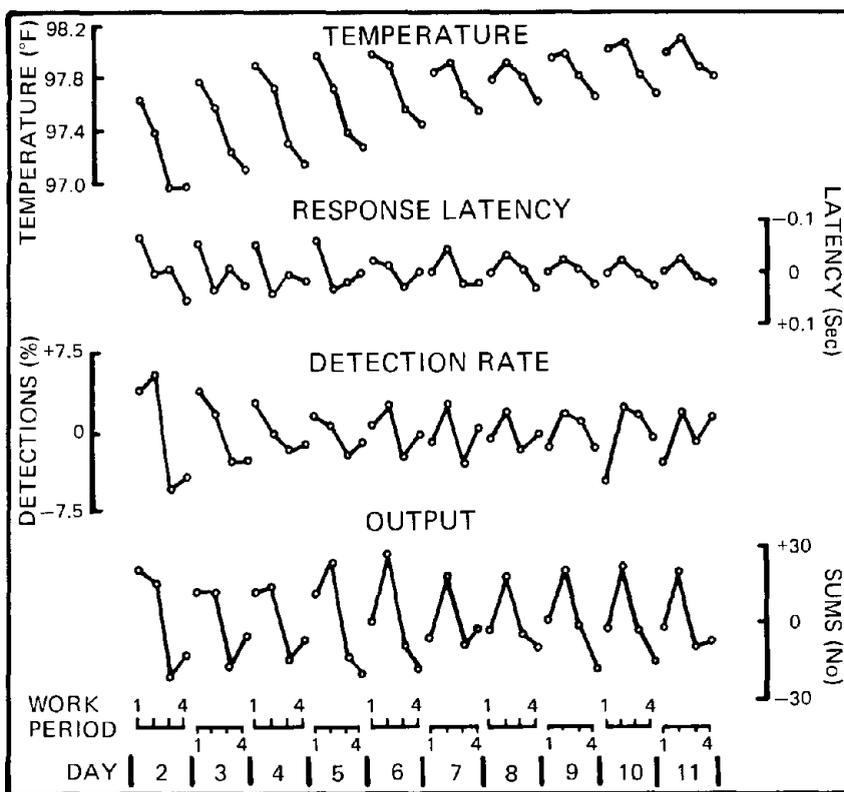


Figure 10. Changes in on-shift trends in (a) temperature and (b) relative variations of three performance measures, over a 12-day period of night-shift working.

I'm reading into this more than I should, I think that here we got more of a change. In fact, the performance pattern has gone way around by the end of the period so that we are now getting a pattern which we would expect on a normal *day* shift.

This last observation allows me to make a comment. A lot of people think that I subscribe to the idea that temperature and performance are *causally* related. I do not necessarily believe this, it's just that we get *parallelism* between the two measures so often that I keep mentioning it. But here is a case where we do *not* get the parallelism; in fact, the correlation between detection rate and temperature was significantly *negative* in this last stage of the experiment so that the changes in whatever is controlling detection performance are obviously *not* caused directly — or at least in any simple manner — by the changes in temperature.

This research was sponsored by the Navy and there was no weekend break because you can't have a weekend break when you're sailing a ship; this was annoying for us, but we had to do what we had to do. However, it's pretty obvious what the effect of the weekend break would be. We know that the adaptation rate is so slow during the first five days of night shift that very little happens. If you have a break at the weekend then you simply go back to square one again and you have the first five days all over. So, although I would like to do experiments on a five-day weekly-rotating shift-system such as you often find in industry, I think we know enough now to predict what we would get without actually doing them.

Little if any adaptation occurs during a normal working week on nights, because the time is not long enough, or even presumably on successive *weeks* of working nights (though there is *some* evidence of more rapid within-week adaptation as you go on and on). This is, of course, because over the weekend you revert to your normal mode of living. This is very relevant to the alleged advantages of "permanent" night-shift working, because so called "permanent" night shift-workers (i.e., people working at nights for perhaps all the time, or maybe six months of the year) are *not* "permanent" at all since they too have their "days off" in which they revert to the normal routine of the society in which they're living. So this is *not* the solution (at least from our particular point of view) because the temperature rhythm presumably also reverts back to normal on these days off, and then has to start adapting all over again when work is resumed.

In any case, as already has been mentioned, new forms of rapidly rotating shift systems are becoming increasingly prevalent, so the numbers of people on "permanent" shifts may be very small in future. One of these new systems goes 2-2-2-3 (two mornings, two afternoons, two

nights and three days off). This one is becoming increasingly popular, mainly for social reasons, because the unsocially-timed shifts only have to be done for two days at a time, which is tolerable. Now we should be able to predict the sort of variations in mental efficiency we should get with this system from the results we got from the Navy system, which is also a (very) rapidly rotating system. We haven't done a full study yet, but Simon Folkard of our group, in cooperation with Professor Rutenfranz and his colleagues in Dortmund, has just done a pilot study on this  $2 \times 2 \times 2$  system.

This was a laboratory study, the people living in the lab the whole period and doing an assembly task for most of the eight hours on each shift. But they also were tested four times during each shift on a task where we were predicting particular results (which I am glad to say we got). The task was to search through pages of lines of random letters, each line containing 20 letters. At the top of each page were printed either two, four or six particular target letters. The subject had to search through each line in succession and indicate, with a tick or a cross, whether or not all the target letters were present in that line. The main score was how many lines were completed in a given time (two minutes). In the simple version of this task (two-letter target) we knew precisely the results that we were expecting, i.e., a very close relationship between body temperature and performance such as we got with the "simple" tasks used in the Naval experiments.

Figure 11 shows that this is what was found: performance followed temperature, I think you'll agree very closely indeed. In fact, this is one of the best examples of "parallelism" we have ever gotten. However, you will see that when you increase the number of letters to be looked for to six, you get almost exactly the opposite result; and in the four-letter case you get intermediate results. We feel very pleased about this because it is exactly what we were predicting, since, by increasing the number of letters to be looked for, one is increasing the memory load and we already have strong evidence that the circadian rhythm of memory is about  $180^\circ$  out of phase with that for most "simple", immediate processing tasks.

Thus, the idea that the picture is all very nice and clear — you just look at the temperature and the higher it is the more efficient you are — is not true. It is quite obvious that this is an over-simplification and we need to look at circadian variation in many different types of tasks, not simply those measuring alertness or reaction time (the classic type of task which I am guilty of using as much as anybody else). We then have to decide which of the abilities represented by these tasks is most critical for causing accidents in any particular situation.

My grand conclusion is that we *must* have more experimental studies because we simply do not have enough basic information at the moment

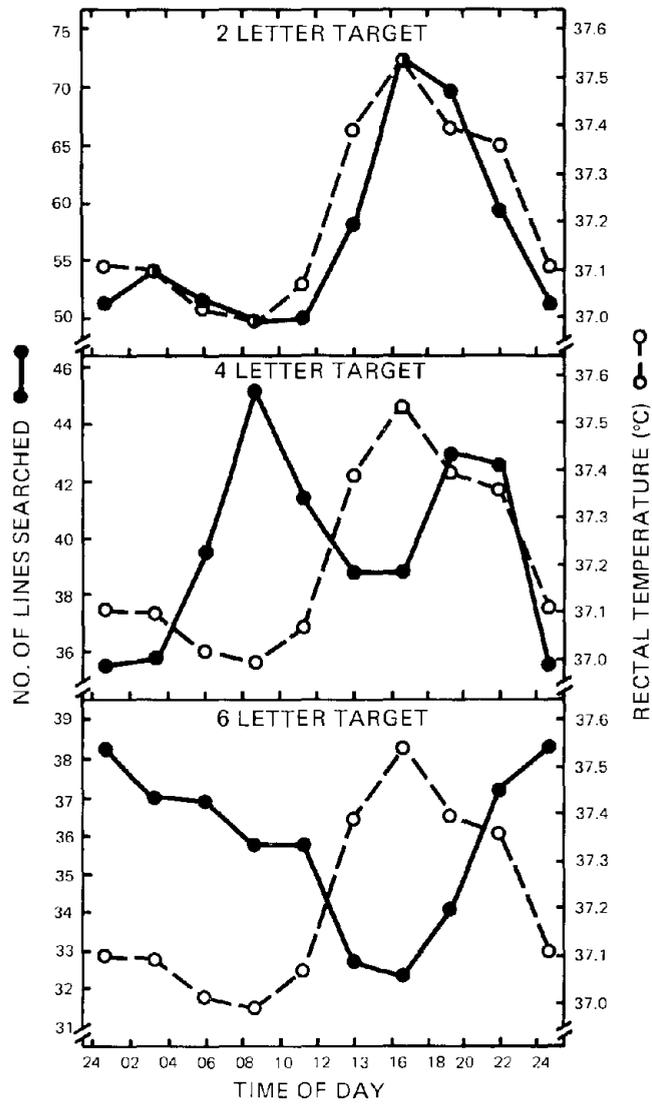


Figure 11. Body temperature, and speed of performance at three levels of memory load in a visual search task, under a  $2 \times 2 \times 2$  shift system.

to say anything really comprehensive about circadian variation in mental efficiency; and, because we don't, we cannot really say anything definite about whether or not "accident causation potentiality" is related to time of day, and therefore to shift work.

## **SHIFT WORK AND HEALTH — AN ERGONOMIC APPROACH: DISCUSSION**

*M. M. Ayoub*

It is apparent from the presentations made by Drs. F. Halberg, H. Levinc, E. Haus, and W. P. Colquhoun that circadian rhythms play an important role in the occupational problems of shift work. However, one must not lose sight of the fact that it would be naive to blame most or all shift work problems on circadian rhythms; rather a systems approach should be applied to show all important factors and their interactions that may lead to better understand and systematically devise studies to solve unanswered problems of shift work.

Analysis of the work system reveals that there are three major components. These components form any Man-Task-Environment-System. The man, the task, and the environment are the basic system components that individually or in combinations through their interactions influence performance, production, safety, and other problems of the system. Table 1 shows a schematic presentation of the components and their important factors, systems performance measures, and design criteria.

In any work situation, the worker characteristics, the task demands, and the occupational environment in combination influence the performance of the system. Therefore, it is necessary, if the injury and illness data show significant increase in the safety and health risk potential of the worker, that needed research be implemented to bridge the existing gaps so that the system behavior can be understood as its components' factors change through their range.

Ergonomics emphasizes the proper match between job demands and worker characteristics, work capacity, and training under various environmental conditions and work organization. Thus it is necessary to develop better methodologies and/or use adequate methodologies now available for: (1) job analysis to determine job demand under shift work situations, (2) worker screening to ensure high productivity with lower accident and illness potential, (3) assessment of the relevant environmental stressors which may act as a catalyst to increase the work load physically, psychologically, and physiologically, and (4) determination of the effect of work

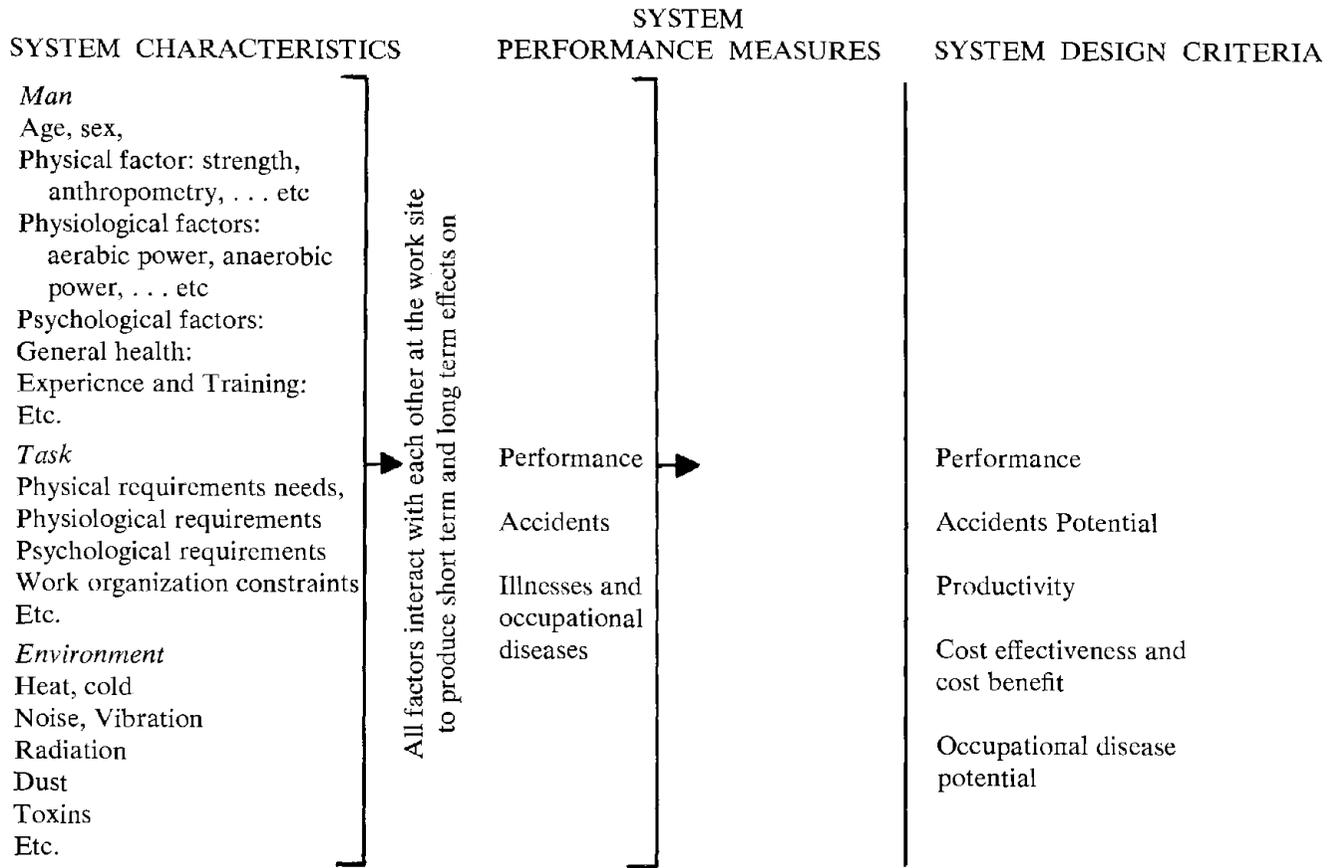


TABLE I  
MAN-TASK-ENVIRONMENT, its components, performance  
measures, and design criteria.

organization in terms of work schedules, rest schedules, and meal schedules, and shift hours and rotation.

This not only applies to shift work, but is also valid for any work situation in which a human is a component of the system. If shift work is approached in a similar way, then it would be possible to identify those systems factors which account for the most change in hazard potential due to changes in hours of work. This can speed the process of closing research gaps to provide badly needed answers.

Another important step which must be initiated now is bridging the gap of knowledge from animal studies to human studies. Parallel studies must be undertaken to ascertain the relationships between findings using the animal model and the human model.

#### *Summary*

It cannot be overly stressed that valid data are essential if, in fact, shift work does increase hazard potential leading to accidents and illnesses, before useful studies can be initiated. Studying a single factor or variable at a time in such a complex problem has shown time and time again to be fruitless. Systems approach to the problem of shift work would result in better identification of factors which may contribute to changes in hazard levels for shift work over types of work schedules for further study.

Unless assessment of worker characteristics vs. job requirements under occupational environment can be approached, combined with novel ideas, methodologies, and experimental design making use of animal studies, it would fall short of the goals envisioned in this symposium.

## **SHIFT WORK AND HEALTH — INTERDISCIPLINARY ASPECTS**

*Torbjorn Akerstedt\**

The objectives of this symposium on shift work and health have been stated as the summing up of existing knowledge in the field, the indicating of further research needs, and the drawing up of guidelines as to how to fill these needs. To this end, other contributors have had the task of comprehensively treating the separate major research areas or disciplines relevant to the subject. This specialization, while necessary, is from the applied viewpoint somewhat disadvantageous. This is so because the endpoint problems, which justify much of the research, consist of and are caused by the interaction of factors belonging to many various research disciplines. This paper therefore will serve as a complement to the preceding discussions, attempting to cut across research areas, to connect and integrate them. In addition, some topics which have emerged as crucial in the research efforts at our laboratory in Sweden will be included.

To begin with, our research objectives should be stated. We have found that the main questions to guide our research efforts can be formulated as follows:

1. Are there processes inherent in the shift work situation that lead to decreased well-being?
2. If so, how do they operate?
3. Which properties of the individual predispose him for developing decreased well-being in shift work (high risk individuals)?
4. Which environmental properties predispose for decreased well-being (high risk situations)?

The concept of "well-being" is used here to indicate that the endpoint of research needs to be a broader concept than conventional "health." One implication of this is that we consider the whole problem area one where interdisciplinary thinking and methods must be applied.

In order to sort out some of the research components, a simple model of psychosocial factors and disease/disability<sup>52</sup> may be used as a

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\*co-authored by Jan E. Froberg

start. This model essentially says that environmental stimuli, e.g., work hours interact with the individual's psychobiological program, e.g., circadian rhythms structure. The subsequent reaction to this confrontation — e.g. stress reactions — may, under certain circumstances, lead to physiological costs and to the endpoint of disease/disability or its precursors. We shall attempt to look at this process with emphasis mainly on present knowledge and research needs. With this intent, our contribution will center on the relation between shift work and endpoints, the process in between, and the interindividual and environmental dimensions of the process.

### *Shift Work and Endpoints*

From the applied point of view, the important connection to establish in Figure 1 is between boxes 1 and 5 — environmental stimuli and endpoints. The studies attempting to do this have of necessity been of the survey/epidemiological character. They have been reviewed elsewhere in the proceedings but in brief they seem to indicate that shift workers have:

- An excess of sleep problems including short sleep time, difficulties of falling asleep and retaining sleep, not feeling refreshed after sleep etc.<sup>85, 31, 35, 28, 44, 61, 11, 78, 56, 3, 23, 60, 84, 81, 16</sup> The problems occur mainly in the night work period and often are associated with tiredness, bad mood, restlessness, digestive problems etc.
- an excess of minor nervous disturbance states.<sup>3, 15, 11</sup> However, when more lasting traits are measured, the differences disappear.<sup>61</sup>
- an excess of gastro-intestinal disturbances.<sup>85, 4, 2, 12, 10, 15, 27, 82, 51, 13, 3, 76</sup> However, some studies have failed to find such differences.<sup>54, 38</sup>
- a lower frequency of absence in some studies<sup>1, 71</sup> and a higher in others.<sup>14</sup>
- the same mortality rate as among day workers.<sup>75, 73</sup>

In spite of the Dirken study<sup>25</sup>, it can be concluded, from a number of the other studies, that those investigations which show shift workers to have an excess of ailments occurring temporarily, and in direct relation to the night shift, receive very strong support. (Dirken found that when the subjects were not aware that shift work problems were investigated no marked excess of particular ailments was found among the shift workers. They, however, exhibited significantly lower overall well-being.) Some authors tend to underestimate the importance of the reports on which the conclusions above are based. The reason is the temporary character of the problems. We think it very important, however, to keep in mind that the problems found are present during approximately one third of the shift worker's working life (the night shift). Indeed, a day-working population exhibiting comparable ailments would cause much concern.

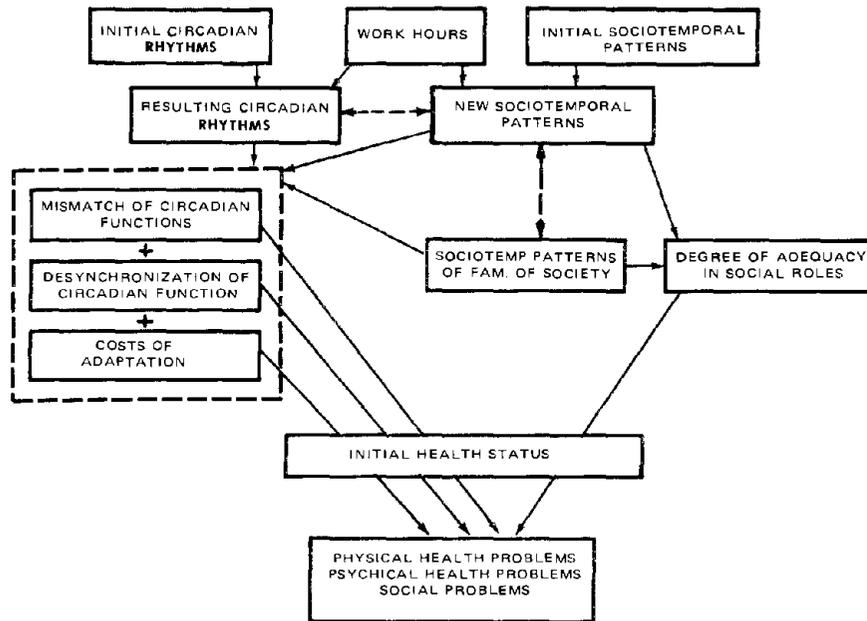


Figure 1. A theoretical model for psychosocially mediated disease. The combined effect of psychosocial stimuli, e.g., shift work (1) and the psychobiological program (2) determines the psychological and physiological reactions (mechanisms (3), e.g., stress) of each individual. These may, under certain circumstances, lead to precursors of disease or disability (4) and to disease (disability) itself (5). This sequence of events can be promoted or counteracted by interacting variables (6). The sequence is not a one-way process but constitutes part of a cybernetic system with continuous feed-back.

As to "disease" i.e. established such, we hold the opinion that particularly gastrointestinal diseases are more frequent among shift workers. Some studies fail to find results to support this. However, the vast majority of questionnaire reports do exhibit such results and, more importantly, those studies which take into account the groups which transfer from shift work<sup>3, 1</sup> also indicate that shift work is associated with gastrointestinal diseases. Andersen<sup>8</sup> gives additional support using objective clinical methods to diagnose ulcer.

Still, results do conflict in many cases and the expected differences between day and shift workers often are rather small. Furthermore, not very much is known about the causal relations in the pathogenic processes. Little advice can be given to those who develop problems in shift work.

On the whole, the state of research on shift work and health is very unsatisfactory. However, the literature does point to what the research difficulties are. The most obvious conclusion is that the research area is very complicated and fraught with confounding variables.

The greatest confounder of all is the selection effect, i.e., individuals unable to cope with shift work who transfer to day work, or who perhaps never even try shift work. The consequence of this is that the transverse studies (i.e. all studies) where simple tabulations of problems for shift and day workers are made, obtain results which are heavily biased in the direction of underestimation of shift work problems. Some of the more careful transverse studies<sup>3, 1, 10</sup> have separated out the transferees and have shown them to form a sizeable part of the day work group. The transferee group have, by the same authors, been shown to have considerably higher frequencies of disease than the groups of "pure" day or "pure" shift workers.

Thiis-Evensen<sup>7</sup> estimates the proportion of shift workers not being able to adapt to shift work at 20%. This figure is based mainly on officially recognized transferees, probably leaving out the unofficial ones. Thus, the 20% seems a rather conservative estimate. In any case, only longitudinal studies can safely control for the selection mechanism.

A further cause of the underestimation of the negative effects of shift work is the attitude of shift workers towards bodily signals of disease. Andersen<sup>3</sup> noted that whereas shift workers did perceive digestive, sleep, or mood disturbances, these were considered a natural part of the job situation. Of the people who complained of various disturbances or were found to have or have had objectively verifiable diseases (e.g. through X-ray), a far greater proportion of the day workers had sought medical help. This implies that in those studies where well-being data is being tabulated, those data concerning the shift workers are likely to produce underestimates. The significance of this is obvious.

As to the measurement of the dependent variables, considerable problems exist. If one wants to investigate whether shift workers differ in amount of disease from day workers, it is not enough to rely merely on subjective reports as has been done in the majority of the studies to date. Many studies can rightfully be criticized on this account. Objective indices are needed. However, in our opinion, it is also important to begin to develop more sophisticated survey instruments.

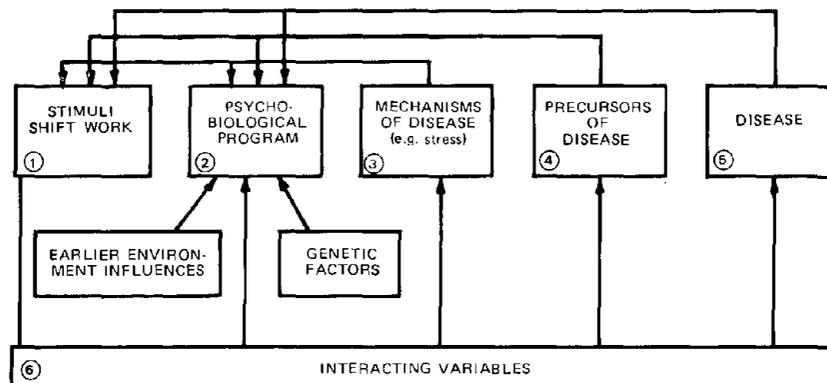
In practically all survey studies, the dependent variables have been treated in a rather crude manner. Frequencies of various ailments have been tabulated and nothing more sophisticated than percentages have come out. As all researchers in the field have agreed on, explicitly or implicitly, the research problems in shift work are multivariate. Multivariate problems, in turn, should be treated with multivariate methods. Most multivariate methods demand measurements to be carried out on

the metric level where each individual can be rated on degree or amount of a certain property. The multivariate approaches called for can come in many shapes, of which the multiple regression techniques stand out as most important. A method which has been found very fruitful at our laboratory is latent profile analysis. This method offers a convenient way of e.g. sorting out groups which are optimally different with respect to their values over a number of variables. Resulting groups are thereafter analyzed with respect to sets of predictor variables e.g. through discriminant analysis.

### *The Process*

What emerges very clearly from research on shift work and endpoints is the great need for studying the process of the pathogenic processes i.e. the intermediate boxes of Figure 1. This is the only way in which we can conclusively establish: (1) whether there is any link at all between shift work and disease, (2) the size of the problem — how great a proportion of the normal population is at risk? (3) which are the properties of the individuals most likely to suffer? (4) which are the properties of the environment most likely to affect the outcome of the pathogenic process?

In an attempt to sort out the main concept involved in the process and to clarify our own thinking, we have worked out the model in Figure 2. Essentially, it shows that the distribution of work hours interact with the individual's initial circadian rhythms to form the rhythm pattern that will be exhibited in shift work. Also, the individual's original socio-temporal patterns together with the patterns of family and society interact to cause the initial problems of shift work. At the same time, the new socio-temporal pattern of the shift worker will interact with that of the



*Figure 2. Illustration of possible relations between the main variables involved in adaptation to shift work.*

family and society and produce various degrees of social inadequacy, which, if considerable, will have effects on psychological as well as somatic well-being. Finally, these social, psychological and somatic problems or "ailments" may, under certain circumstances, develop into more serious and permanent states of ill health and low well-being.

The model was developed to visualize the areas which seem important to us and particularly to point out which possible connections should be studied. This means, of course, that the model is highly speculative. However, if these links between shift work and well-being are to be investigated, it will be necessary to complement the present research approaches. What is needed can be classified according to the following dimensions:

1. *Prospective studies.* A transverse study uncovers no mechanisms, only associations. A prospective study covers the "before," the "during" and maybe also the "after" stage of the shift work experience, i.e., the basic sequence needed to sort out cause-effect links. This also makes for control of the selection effect. To date, no study of this kind has been carried out over any length of time.
2. *Intensive studies.* The large scale survey-type of studies are important. However, in order not to leave a "black box" of unexplained mechanisms and to achieve more objective support for studies relying on subjective indices, intensive measuring is a necessity. With the concept "intensive" we refer to thorough and often repeated medical/psychological check-ups but also to the very close psychophysiological monitoring carried out in studies on circadian rhythms. This approach has been used to a limited extent, mainly in investigations on circadian rhythms.
3. *Experimental studies.* It is almost trivial to claim that the experimental or semi-experimental approach is the only way to reveal causal links. However, it is important to recognize that experiments can be performed not only on the intensive level but also on the survey level. Neither has been used to any extent.

#### *The Core of the Process — Circadian Rhythms*

Shift work is a problem because it disturbs social, psychological or physiological 24-hour temporal patterns. Because of this, we feel that circadian rhythms make out the central core of the process. Accordingly, all attempts to carry out research on shift work problems should, directly or indirectly, center on circadian rhythms. The basic knowledge on the subject has been covered elsewhere in the symposium so we shall repeat only that the main finding of research is that a great number of physiological and psychological functions exhibit circadian rhythms (for a review see e.g. 22). This includes many of those rhythms which are particularly important to our objectives, such as rhythms of physiological or psycho-

logical activation/arousal, metabolism, and digestion. The second important finding from this area of research is that circadian rhythms under optimal conditions need between one and two weeks to adapt (invert) to night activity.<sup>86, 59, 70, 74, 36, 45, 9, 80, 40, 43, 66, 43</sup> The third important finding is that shift workers do not live under "optimal conditions" i.e. when homogeneous synchronizers strive in the same direction. Due to the conflicting synchronizers, the shift worker retains his day-oriented circadian pattern with only minor deflections like flattenings of curves during the night shift period.<sup>58, 79, 82, 42, 23, 17, 6</sup>

Biological rhythm research cannot, as yet, offer much more information than this. Much knowledge remains to be collected. To begin with, the relations between physiological and psychological arousal functions are still much in debate. To judge from modern studies, however, one should be able to conclude that there exist in circadian settings *gross* relations between physiological and psychological activation.<sup>49, 17, 68, 57, 33, 18, 19, 20</sup> With this knowledge, together with the other findings, the nightly trough of circadian functions can be used to explain the well-known small hours fatigue during the night shift. Part of the sleep difficulties during the day can be explained by the reverse — going to bed when alertness functions are rising.

Important contributions in this area have been made through electro-physiological studies showing day sleep to be different (interpreted inferior) from night sleep in many respects.<sup>69, 20, 53, 24, 50, 37</sup> Also, some of these authors have begun to seek an answer to which factor — the circadian rhythm or external noise — explains most variance in sleep problems.

On the survey level, Aaronsen<sup>1</sup> noted that some individuals developed sleep problems in spite of "good housing." This was particularly frequent among transferees before the transfer. On the whole EEG studies seem to indicate that despite nice and quiet sleep conditions, sleep during the day still differs (interpreted inferior) from its counterpart during the night. Efforts to reach conclusive results in this area are very important. In Europe, several such studies seem to be under way. Another, more general, topic investigated by sleep labs concerns the implications of disrupted sleep patterns, or simply the answer to the question: what is good sleep?

Another great issue on the circadian level is the biological costs of adaptation. As yet, we have no knowledge about the long term consequences of particular "disturbed" circadian patterns. What e.g. are the implications of the transient desynchronization that takes place in adjustment to night work? Theoretically, breaking the homeostatic requirement of the right substance at the right spot at the right time could have serious consequences. This issue has seen practically no research effort at all.

One very intriguing, yet isolated, finding is that of Lund<sup>85</sup>, who discovered that those individuals who develop desynchronization during isolation free-run (those carried out by the Aschoff group) experiments were the same individuals who scored high on neuroticism and psychosomatic disturbances scales. An evaluation of the short and long term implications of changes in circadian parameters is badly needed.

A second cost aspect is that of "wear and tear" on the organism as a consequence of repeated attempts to adjust or simply of being active at times when physiological preparedness for activity is at its nadir. Very few studies exist. There are, however, some studies in which attempts have been made, and they point to increased energy expenditure during night work.<sup>83, 88</sup>

At our laboratory, we have performed experimental studies on temporary night work. Our recent (as yet unpublished) findings indicate that inexperienced night workers react with elevations of urinary adrenaline excretion, serum cholesterol, serum uric acid, serum glucose and other substances. Such a reaction we interpret in terms of higher energy expenditure and catabolism. An interesting additional finding in our study was that a change in secretion of gastrin (gastric juice releasing factor in stomach) was rather closely related to changes in psychosomatic well-being. A decrease in gastrin on the night shift was related to a decrease in psychosomatic well-being. The results are being analyzed further. These few studies need much more confirmation and the only way to do that is through similar, intensive studies on comparatively large samples followed longitudinally. Our own results indicate the necessity of including the subjective experiences paralleling the physiological changes.

A third cost aspect is the long time consequences of being active during the portions of the 24 hours when the resistance to noxious agents is lowered. Most investigations in this area (see e.g. review 90) have been concerned with susceptibility of animals to agents like e.g. white noise, ouabain, ethanol etc. Often dramatic variations of mortality have been found as a function of time of day. On humans, the stimulus and response variables have been less dramatic but the conclusion from animal studies has been supported. Obviously, these results can, in the longer perspective, be of importance for shift workers but no studies have been carried out.

With respect to sleep deprivation, results from both survey and intensive investigations are in agreement: shift workers get less sleep when on night shift. It is very likely that prolonged moderate sleep deprivation, in certain circumstances, may lead to mood changes, nervous problems and difficulties of role fulfillment. Sleep deprivation has furthermore been suggested to be the cause of most shift problems.<sup>1, 16</sup> So far, however, no causal links have been established. We can only note that the answer once

again necessitates longitudinal/prospective studies in combination with experimental designs.

### *The Interindividual Dimension of the Process*

One of the most fascinating aspects in the research on shift work problems is that of interindividual differences. This is important from two points of view. First, individuals differ in their reactions to shift work, and in order to better understand results from large groups of subjects, keeping track of the separate individuals is necessary. Second, in trying to predict outcomes of attempts at adjustment interindividual monitoring is, of course, a prerequisite.

On the basic circadian level, Kleitman<sup>48</sup> reported interindividual variation in curves to be explained by reference to concepts like evening or morning alert types, i.e. phase differences. Those who have studied phase differences in circadian rhythms<sup>63, 64, 65, 67, 42, 34</sup> generally have found that so called morning active "M" and evening active "E" individuals differ in phase both in physiological and psychological aspects of circadian rhythms. In pilot studies at our laboratory, we have obtained similar results. Other individual differences in this area are those of level, amplitude and stability of curves. These aspects have received little research interest as yet.

Albeit important, intensive circadian studies are cumbersome and it must be of importance to try to catch some of the circadian properties in questionnaires or rating scales in order to include the circadian factor in survey studies. Oquist<sup>89</sup> and Pátkai<sup>64, 65</sup> have developed such scales. Oquist has made a rather elaborate evaluation of his scale, and, among other things, found it to consist of two dimensions — morningness/eveningness and "capacity for wakefulness." Ostberg presently is using<sup>87, 88</sup> and evaluating a modification of the Oquist scale and we ourselves are trying to develop improved scales of the same kind.

Our preliminary results point to the same dimensions as those Oquist found. Profile analysis of the questionnaire also yielded a grouping of individuals into four main groups: morning alert/evening tired, morning tired/evening alert, morning alert/evening alert, and morning tired/evening tired. These results have to some extent been validated by intensive circadian rhythm studies. Thus M- and E-types differ in circadian patterns of catecholamine excretion and subjective arousal. Other questionnaire approaches appear to be at hand both in Europe and the U.S.

As to the predictive use of circadian characteristics, it is reasonable to expect that people differing greatly initially should differ also on rate and type of adaptation to inverted rest/activity cycles. Thus, it can be hypothesized that individuals with low amplitudes, having "less to invert," adapt more easily. With respect to M/E types, Aschoff<sup>67</sup> and Hoffmann<sup>43</sup> have suggested and given some empirical support for the idea that M-types have shorter circadian periods than the E-types, thus are better adapted to

our normal 24-hour period. To some extent, Hildebrandt<sup>42</sup> has substantiated this by showing that ergotropic individuals tend to have shorter spontaneous periods than trophotropic individuals. He also observed that these ergotrops were those who showed the fastest increase in physiological activation in the morning i.e. they were M-types.

In our pilot studies we have obtained similar results. Furthermore, in the free-run experiments carried out by the Aschoff group it regularly turns out that all individuals become M-types when synchronizers are removed, i.e. they tend to wake up from sleep much closer to their circadian acro-phase than is usually seen in normal life on 24-hour schedules.<sup>8</sup> A tentative interpretation of this may be that E-types, having periods considerably longer than 24 hours, continuously have to adapt to our normal 24-hour period. They have to go to bed when not sleepy and to rise while still very much sleepy. Their circadian rhythms seem to be "trying" to break out of the too short 24-hour period. In fact, one might say that these persons really need a work schedule that rotates or floats in comparison to our normal 24-hour rest/activity span. E-types probably would be better off if they could postpone going to bed and rising 1-2 hours. From this reasoning, a fair guess would be that the E-type individual would have less problems adapting to night work. Ostberg has shown that this to some extent appears to be the case.<sup>88</sup> In his studies, M-types showed greater nightly decrease than E in most of the indices of fitness and adaptation that were used.

Ostberg also found that E-types spontaneously changed their routines more (were more flexible) than M-types when on night shift. In this context, it is interesting to note that M-types have been shown to be somewhat more introverted and rigid in personality.<sup>63, 65</sup> Still, the differences between the two circadian types are not all that dramatic and these promising attempts need much additional elucidation, particularly from studies where subjective and objective costs of the adaptive behavior of the two types can be evaluated.

Even more important is the application of prospective survey studies where individuals with certain key circadian properties are monitored over a considerable time with respect to subjective well-being and preferably also objective indices of potentially pathogenic mechanisms e.g. catecholamine excretion, serum lipids, uric acid, physical work capacity, immunological parameters etc.

It is of interest to note that Andersen<sup>9</sup> found that diurnal type may be an important pathogenic factor as a disproportionately large part of the transferences from shift work turned out to be M-types. We have ourselves begun to include questions on circadian type in our shift work questionnaires. From what appears from our first transverse pilot studies, M-types exhibit particular difficulties in day sleep although the

differences are not very marked. We also are presently starting up a longitudinal study in which the circadian aspects are included in the questionnaire. Here, we hope to receive information on the predictive power of circadian type as estimated by questionnaire method.

Another related subject concerns the individual's capacity for wakefulness or rather need for sleep, which can be expected to be of great importance when coping with the problems of adjustment to the night shift. However, no prospective or other studies of this aspect are on record so far.

Other interindividual differences also are of importance, the most obvious of which is the initial health status of the individual before he enters shift work. Thus, nervous problems, sleep problems, gastrointestinal problems as well as diabetes and epilepsy are generally considered reasons to advise an individual to avoid taking up shift work. The validity of this practice, although widely applied, has not been systematically investigated. In our own longitudinal survey approaches, we are including the first three factors in our questionnaires.

Häkkinen<sup>22</sup> found in a transverse study that extreme groups with respect to adaptation to shift work differed in number of children, psychosomatic tension, sociability, attitudes etc. Adapters had fewer children and in general more "positive" scores in the indices. Nachreiner<sup>23</sup> divided shift workers into high/low introversion and high/low neuroticism groups. Not surprisingly, those high in neuroticism exhibited most problems in shift work. Interesting as such transverse studies may be in pointing towards associations, they hardly can establish causal relations.

Age is another important factor about which few circadian studies (on adults) have been carried out. However, in survey studies there often has been shown that problems of well-being increase with age but that attitudes tend to improve. Also, sex may be important in determining adjustment to shift work. For female workers their second role at home may add to the difficulties of work hours. This problem is presently being investigated by several groups in Sweden.

Apparently much knowledge on the interindividual level remains to be collected. To do this is very urgent as one of the main tasks from the applied viewpoint must be to predict who will and who will not manage to adjust to shift work.

#### *The Environmental Dimension of the Process*

The other important dimension besides interindividual differences is the environmental influences. The central factor here is, of course, the type of shift schedule. From reviews of research on circadian rhythms, Teleky<sup>24</sup> concluded that long rotations should be employed in order that the body be given time enough to adapt to inverted schedules. However, we know that even for permanent night workers, circadian patterns never

really invert completely. And for rotating shift workers, inversion is even less likely. Furthermore, in many western societies, permanent evening shifts are forbidding to most individuals, and short spells shorten this distress. Instead, today the trend seems to go towards very short two or three day rotation, replacing the usual weekly rotation. The fast alternative also seems to carry the advantage of demanding very little circadian adaptation, thus avoiding a build up of sleep deficit and physiological costs. On the other hand, exposition to night work is more frequent, the implications of which are unknown.

At the extreme end of this scale of rotation, speed is the irregular system seen particularly in transportation. There, the possibilities of circadian adaptation are practically nil. Some studies on transportation personnel have been carried out and the results indicate considerable sleep problems, to some extent verified through electroencephalographical recordings.<sup>28, 29</sup> Another study<sup>42</sup> investigated the interaction of length of work hours and circadian rhythm on a group of train drivers.

It was found that the higher the load in hours the more pronounced grew the amplitude of the circadian curve of performance. In particular was this true for the afternoon dip in performance which became very deep. The implications for transportation are obvious. In any case, it is urgent to study systematically the effects of type of schedule both with respect to circadian changes and to broader evaluations of consequences to well-being. Effects of extra time for recovery after the night shift is a related question.

At present, in one of the studies at our laboratory we are trying to follow a group of workers who are reverting from three-shift to a double day system and another group which is changing from double day to a morning-night shift schedule.

Another central issue already touched upon above is the relative effect on day sleep of the circadian arousal rhythms in comparison to the noise from the environment. Also, eating habits in shift work presumably are of great importance in the development of digestive disturbances. How, what and when to eat can only be decided through controlled experiments. No such study has been carried out, although Ostberg<sup>87</sup> touched the problem when he showed that M-types reached their 24 hour consumption limit earlier than E-types and that they also tended to decrease their consumption more while on the night shift.

Finally, a very important environmental aspect must be the physical or mental demands inherent in the occupational tasks. Not very much is done in this area either. However, Klein<sup>46</sup> showed that adaptation went faster in groups allowed to be active and more in contact with the environment. It seems reasonable that heavy physical work load would contribute to the increase in level of the night sections of circadian

rhythms and also to make the individual more tired, thus making it easier to sleep. On the other hand, biological costs of work when physiological preparedness is low presumably will increase with increase of work load. However, these aspects have not been studied either on the circadian or on the survey level.

In this context, it is interesting to note some of the studies on sickness absence. Taylor<sup>72</sup> studied refinery workers (light work) and found that shift workers exhibited far less absence than the day workers. In contrast, Brandt studied individuals with moderate to heavy work and found the reverse. It proves nothing but indicates the need for systematic investigation of work load effects both on intensive and survey levels.

### *Social Factors*

As noted in the introduction, it is well established that shift workers suffer from a host of social handicaps. This, of course, is a very important fact in itself and needs assessment in terms of practical implications of disadvantages with respect to family life, friends, leisure activities, possibility to make use of the services society offers day workers, and last but not least participation in the democratic process of society. A large scale investigation of these issues is being undertaken by social psychologists in Sweden.

In theory, the social handicaps that shift workers suffer also can be expected to affect psychological aspects of well-being, e.g. anxiety, tension, self-esteem, and similar parameters. As noted earlier, Mott<sup>61</sup> did not obtain results to support such a hypothesis. This may be yet another case of the selection effect. What he did find, however, was that those individuals who felt that work hours interfered with their role behavior also showed psychological and psychosomatic disturbances. This effect, or rather association, also seemed to be indirect in the sense that not only being away from work, but also being too tired when at home, interfered with role fulfillment. The sequence in which these events develop and their causal links are difficult to determine. Still, skillful use of longitudinal follow-ups may clarify some of the relations between degree of role fulfillment and the psychological/somatic maladjustment.

The why aspect and the interindividual differences in social reactions are all the more important as Mott<sup>61</sup> showed that the role fulfillment factors carry by far the largest explanatory power in predicting the variation in the global attitude to shift work. This important question is really worth a study all by itself. Is it e.g. the case that this great importance of the role fulfillment variables is coupled to the selection factor?

Have those individuals who have most psychosomatic problems been transferred, leaving too little variance left? It would be very interesting to see a study on the relative weights in a population of transferees. In this group it is not unlikely that health aspects will carry heavier weight.

### *Summing Up*

There remains a tremendous lot of work to be carried out before the basic questions about shift work effects can be answered. What we have wanted to emphasize in this paper is the interdisciplinary character of the research tasks. The circadian rhythms carry (in this context) very little importance in isolation without relation to each other or to health. Likewise, disordered patterns of circadian rhythms have to be evaluated against valid indices of well-being. The concomitant biological, psychological, and social costs of adjustment attempts must be studied, also. Particularly important are the modifications of the pathogenic process brought about by interindividual and environmental factors.

This demands that investigations should be carried out both on intensive levels and on survey levels. More importantly, however, these studies need to be carried out in prospective or at least longitudinal designs. Where possible, experimental approaches should be used, also. If efforts along these lines are not made, the pathogenic process will remain a speculation. Experiments, it should be emphasized, are perfectly feasible even in strictly sociological studies.

Too many sociologists and social psychologists are satisfied with descriptive and associative studies where experiments would be applicable. Spontaneously occurring experiments are taking place all the time and offer great opportunities for evaluation.

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## **SOCIAL-PSYCHOLOGICAL DYNAMICS IN SHIFT WORK: DISCUSSION I**

*Robert D. Caplan*

Dr. Torbjorn Akerstedt has touched on a number of important theoretical and methodological issues in his presentation on programmatic research perspectives on shift work. I intend to underscore some of these points and introduce some related findings. I will conclude by mentioning a couple of ideas for assigning people to shifts that might be tried out on a pilot basis by practitioners in work organizations.

### *Interpreting Individual Differences*

A major premise of the model that Torbjorn Akerstedt has just presented is that one must consider the fit between the person and the environment. In the study of shift work this translates into the fit of the psychological and biological rhythms of the person with the rhythms of the day or the fit between the abilities and needs of the human and the demands on those abilities and supplies to meet those needs from the environment.\* In this regard, one is no longer searching for some simple answer to whether or not shift work is good or bad because studies cited by Dr. Akerstedt suggest that shift work may fit some people's constitutions and may misfit others.

The question arises as to which type of person-environment fit is most predictive of health and of safety-related behavior: the perceived fit as reported by the employee or the objective fit as observed by the scientist. It would appear that most studies of shift work have looked primarily at the latter.

*Objective Versus Subjective Environments.* Although many of the studies on human shift work do suggest individual differences in adapta-

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\*Several general theories of human behavior also have been guided by the premise that behavioral, psychological, and physiological responses of the person are a function of the interaction or fit between the person and the environment (Lewin, 1935; Murray, 1938; Pervin, 1968; and French, Rodgers, and Cobb, 1974). Paul Mott (Mott, Mann, McLoughlin, and Warwick, 1965) also has commented on how the ability to adjust, a person characteristic, determines whether or not shift work, an environmental characteristic, produces health-related problems for the workers.

tion, there still are some questions to be resolved regarding the dynamics of the adaptation process. For example, Dr. Akerstedt cited a study suggesting that persons already in neurotic, highly anxious states may be more likely than relatively normal persons to react to phase or time shifts in their work day by showing desynchronization of their biological rhythms. It will take further research to determine the extent to which there are or are not hormonal correlates of these emotional states which produce the desynchronization. It also will take future research to determine whether desynchronization is largely a result of how highly anxious persons, compared to nonanxious persons, perceive and interpret the objective environment in which they work.

Assessments of how people subjectively perceive their shift work environments as compared to the objective nature of the environments may help us answer these questions. Perhaps anxious individuals become so withdrawn in their perceptions of their environments that they have difficulty perceiving that a night shift is their working hours, the time when they must be at peak performance. The result may be prolonged desynchronization. If we can fathom these subjective perceptions, we may be able to provide special cues for these people that help them set their bodies in phase with their work hours.

Such distortion of the objective environment is a known phenomenon as any psychotherapist can relate from his or her own work with defensive clients. We also have seen this distortion in studies which compared the relationship of objective and subjective stresses to human strain. One study obtained observations of three hours' work for white collar professionals tallying phone calls and office visits as an objective measure of quantitative work load.<sup>6</sup> At the same time the pulse rates of these men were telemetered and a cholesterol assay was derived from a blood sample taken at the end of the three-hour period. Then the men filled out a self-report or subjective measure of their work load. The objective and subjective measures correlated .68 but partial correlation and multiple regression analyses indicated that all of the relationship between objectively measured work load and pulse rate could be accounted for by subjective perceptions ( $R = .68$ ). Both objective and subjective measures of work load independently predicted to serum cholesterol ( $R = .46$ ).

Another study<sup>10</sup> compared objective versus subjective measures of role conflict among white collar employees and found that the subjective measures were superior in predicting to an index of employee job-related tension.

The point of these studies is that subjective perceptions can sometimes be more important than the objective reality in determining physiological and psychological health-related states. Often it is not the environment but how the person sees that environment which can deter-

mine health and health-related behavior. Some of these distortions may insulate people from the known health-related effects of shift work and others of these distortive mechanisms may not. Research, however, must be conducted to better understand what role, if any, subjective perceptions of time and the interpretation of phase shifting has on health and its indicators.

*E-types and M-types.* Another finding cited by Dr. Akerstedt deals with the distinction between E-type (evening, owls) and M-type (morning, larks) people. Here again, there is occasion to consider the goodness of fit between the characteristics of the person and the nature of the shift that is worked by the employee. The E-types appear to be extroverts, just as Eysenck<sup>5</sup> has found. They are outgoing, and they like to be around other people. Schubert<sup>15, 16</sup> has studied a group of people who appear to be rather similar to the E-type. He calls them "arousal seekers." Compared to the arousal avoiders, arousal seekers prefer rather than dislike loud parties, roller coaster rides, soup with vegetable chunks rather than pureed soups, smoking, drinking, and other sources of stimulation.

It may well be that E-types are really quite similar to arousal seekers. Whereas arousal avoiders are believed to *overestimate* the magnitude of stimuli (and hence become satiated quickly), arousal seekers are believed to *underestimate* the magnitude of stimuli and to want more stimulation when everyone else has had quite enough. E-type persons are hypothesized to prefer a day which is somewhat longer than 24 hours whereas M-type persons appear to prefer a 24-hour day or a day perhaps somewhat shorter. Perhaps the explanation of these preferences is that the E-types are *underaroused* by the amount of stimuli they receive in a 24-hour day whereas the M-types are overaroused by a day that extends into the hours of the night shift.

The health-related implications of E- and M-types in shift work settings are far from understood. For example, do E-types really show better adaptation in terms of health to real, nonlaboratory night shifts compared to M-types? If night shifts provide too much arousal for M-types, can part of the problem be solved by placing these people in environments with relatively low arousal (the absence of loud noises, flashing lights, lots of people, and so forth)? Do these traits have any bearing on how people adapt in terms of health and performance to rotating shifts? Only further research could answer these questions.

*Environmental Buffers.* Studies of individual differences focus primarily on which type of person can adapt to which type of shift work environments. One also can take a slightly different approach and ask which types of environments might fit all individuals? Can environmental supports be built into work settings, for example, that will help people withstand some of the demands placed on the individual by shift work?

Dr. Akerstedt has cited research from The Laboratory for Clinical Stress Research which showed that the disruption of life patterns by the introduction of shift-like environments can affect serum cholesterol and serum glucose, both risk factors in coronary heart disease, and serum uric acid, a disputed risk factor. Are there ways in which these potentially harmful effects of shift work conditions might be buffered and rendered harmless?

There are now a couple of studies suggesting that environmental demands which effect physiological strains such as cholesterol and glucose can be buffered by the presence of social-emotional support. In a cross-sectional study<sup>2</sup>, relationships between job demands such as work load and contact with persons in other territories of the organization were associated with high levels of cholesterol, glucose, and cortisol only for persons who reported low social support at work.

In a longitudinal study<sup>4, 5</sup>, cholesterol levels that were initially high as men lost their jobs in a plant shutdown, returned to near normal levels in subsequent months of unemployment but only among men who reported high levels of social-emotional support from family and friends. If management practices introduced supportive work relationships on certain shifts which tended to produce physiological strain, would this have the effect of reducing the levels of those risk factors which Dr. Akerstedt's findings suggest might become elevated during work in a phase-shifted environment? Again, such questions can only be pursued by further studies.

There may be other characteristics of work that also can buffer some of the potentially disruptive effects of shift work. For example, the previous speaker reported on studies which suggest that engrossing, nonboring work is less likely to produce disruptions in bodily functions compared to work which does not make adequate use of a person's abilities. A recent NIOSH study of 22 occupations (Caplan, Cobb, French, Harrison, and Pinneau, in press) suggests that inadequate use of people's abilities is one of the major predictors of dissatisfaction with work and of feelings of boredom. Perhaps use of abilities, opportunities to participate and some element of control over one's work procedures might prove to be compensations that would make work more engrossing for persons on shift work schedules. The appropriateness of these speculations must be judged by further research and by the ability of organizations which put people on shift work to apply the products of any such research.

#### *Methodological Issues in the Study of Shift Work*

*Longitudinal Studies.* Torbjorn Akerstedt has called for longitudinal studies because the cross-sectional research has provided us with relationships which are often difficult to interpret. For example, although some studies indicate that older workers adjust less well to work on night shifts compared to younger workers, the cross-sectional nature of these studies

makes the findings difficult to interpret. Usually persons on the night shift have the lowest seniority compared to persons on the day shift because union-management contracts frequently are drawn up along these lines. Consequently, if one finds older workers on the night shift, are they complaining because they are having difficulty adjusting to the shift or because they have low seniority and are having difficulty adjusting to a new job?

Even though longitudinal studies take us a step further towards the inference of causal relations, they too have their problems. If you follow people over time who enter a shift when they are young and leave and move to another shift when they are older, the changes in their psychological attitudes and bodily functions may be a result of age-related factors as much as they are a result of changes in the nature of the shift. Counterbalancing so that some people change from night to day shift whereas others, drawn at random, change from day to night is only a partial solution because it is possible that people always prefer the first type of shift they are on to the new shift that they entered or vice versa. Furthermore, there may be differences in human reactions depending on whether the person moves from a night shift to some other shift or vice versa.

Finally, such designs are best executed in a set of organizations which operate in relatively stable environments over the course of the longitudinal study. If the environment of the organization (e.g. market conditions, the type of products, the technology, the management or nonmanagement work force) changes markedly during the study, then unwanted nuisance variables may be introduced which confound the particular effects under investigation (Campbell and Stanley, 1963 provide an excellent treatment of some of these problems). Locating organizations with stable environmental conditions, however, is becoming more and more difficult in our rapidly changing societies.

*Laboratory Versus Field Studies.* One possible solution to some of the weaknesses of longitudinal field studies is the use of laboratory situations. Such a study will emphasize *internal* validity by holding various nuisance variables constant or by carefully controlling them. Consequently, we can look at people on fixed shifts, rapidly and slowly rotating shifts, and so forth. We can hold constant changes in the technology, management personnel, union contracts, and market demand for productivity. There is also no reason, however, why some of these variables might not be varied systematically. For example, one can conduct studies of people working different shifts and shift patterns with and without supportive supervisors and with and without coworkers, loud noises, rapid recycling time in the job procedure, mental work, physical work, interpersonal work

(negotiations, personnel decisions, team problem solving), demands for concentration, and so forth.

The more of these context variables which can be introduced and varied systematically, the more likely that the laboratory experiment can overcome one of its prime weaknesses — the inability to provide external validity or generalization to conditions outside of the laboratory. The fewer of the context variables which can be examined, the less likely that the research will help practitioners decide what to do in factory A or company B. Clearly, both internal and external validity are required to provide a useful data base for the practical application of findings.

There will be some types of questions, however, that cannot be answered in a laboratory. Mortality and morbidity data hopefully cannot be gathered on humans in the lab. While such data can be gathered on non-human species, there arises the question of external validity to humans. Are the metabolic processes in the species being compared similar to processes found in humans, and does the ability to use language as a mediator and interpreter of events differentiate the psychoendocrine reactions of human from nonhuman species? These are questions that must be answered before we can fully interpret animal research. Even if the mechanisms producing atherosclerosis or high blood pressure are found to be similar to humans in certain classes of species, there still will be problems in studying human psychiatric disabilities in nonhumans.

*Overcoming the Weaknesses of All Designs by Capitalizing on Their Contributions.* Each methodology can provide a slightly different slice of reality and some slightly different problems in interpreting reality. Perhaps the best strategy is to use a multi-methodological approach for confirming hypotheses about shift work. One could attempt to demonstrate that cross-sectional survey, longitudinal field, and laboratory research all tend to show *convergent* findings.

Consider the problem of trying to gather cardiovascular mortality and morbidity data on the effects of certain shift work conditions. The samples required for such data must, of necessity, be very large because of the small percentage of persons who develop any specific illness or die of it *and* who must also fit into one of the shift work job conditions of interest in the study.

A national health survey, however, could provide some indication of whether or not people with certain histories of shift work were over-represented in certain disease groups. This survey would be partial support for the hypothesis that certain types of shift work lead to poor health because we could not be certain of the uniformity of the criteria used to diagnose different disease entities. Nor could we be sure of the complete nature of the person's occupational and medical history prior to entry into the shift work condition.

In conjunction with such a study, one could conduct cross-sectional and longitudinal surveys of persons on various types of work shifts in which various risk factors of the illness were gathered (such as cholesterol, glucose, and so forth). If these risk factors for disease entities also varied across types of shifts in a manner similar to that found in a large scale epidemiological survey, you would have further support for the hypothesis being tested.

Then one could perform laboratory studies in which the key elements believed to be at work in shift conditions of interest were systematically varied, again examining the same risk factors as were examined in the surveys. The surveys would provide some indication of some of the context variables which might have to be present to increase the external validity of the design (e.g. working in teams or alone, with or without close supervision, and so forth). Again one would look for agreement with studies using the other methodologies.

Finally, one might decide to conduct some studies on nonhuman species selected for their physiological similarity to humans and for their ability to develop, relatively rapidly, diseases of the kind implicated in the large-scale epidemiological studies, and smaller cross-sectional and longitudinal surveys of the effects of shift work on risk factors. Again, the introduction of various context variables might be considered to simulate conditions that might accompany shift work conditions in our societies (such as the presence of friendly versus hostile rates to represent new versus old work groups for the "employee" who rotates shifts).

Now consider putting the findings from such a series of studies to work. Any responsible scientist, regardless of discipline, would be unwilling to assert that his or her particular study completely sewed up any questions posed by practitioners in work organizations regarding shift work. It would also be unlikely that findings developed solely from one methodological approach would ever carry enough weight to be persuasive to persons interested in application for there always would be detractors taking issue with each approach just as there are sometimes vanguards of an approach. An integrated set of findings, however, might persuade some people in work settings to act on the basis of scientific knowledge.

It is much easier to describe such a seeming utopia of research than to build one. To pull off such a set of integrated studies requires a programmatic framework within which epidemiologists, sociologists, psychologists, and physiologists can work under the same roof. Dr. Akerstedt's organization, The Laboratory for Clinical Stress Research, headed by Lennart Levi, promises to be one of the outstanding examples of such a program.

#### *Managerial Technologies for Dealing with Shift Work*

From 1913, when Henry Ford introduced the machine-paced assembly line, until the early 1970s when Saab and Volvo introduced an alter-

native, team-oriented modular assembly, marks a period of roughly 60 years. Shift work has been around considerably longer because there are accounts of shift work as a social concern going back to the 13th century.\* For the reader who is interested in application rather than in further basic research, patience may be wearing thin by now. Consequently, I should like to offer a few suggestions that may be of use. I hope you will keep in mind that we have limited knowledge of shift work and its effects on humans, and therefore the suggestions should be taken as food for thought rather than conclusions.

*Participation.* The majority of collective agreements in large industries have some provisions regarding shift work (U.S. Department of Labor, 1959). Seniority probably is the most overriding criterion for the assignment to shift. Nevertheless, there is evidence that people may vary in their ability to adapt to different types of shifts and shift work and that this adaptation may involve factors which have an imperfect relationship with seniority. For example, there are individual differences in the periodicity and adaptability of circadian rhythms, in whether or not the shift offers a desired opportunity to be away or close to family and spouse, and in the distance one must travel to work. There are probably a number of other factors which also affect people's preferences.

One way to deal with these differences is to attempt to identify all of the relevant traits and place people in shift schedules accordingly. It is unlikely that such a procedure could be very efficient or easily implemented.

Allowing people to participate in deciding which shift pattern or hours of work they would like might be an easier way to allow self-selection to take place. The mechanism of participation can be seen as a fundamental environmental change just as changing the noise or lighting level is an environmental change. Attempts to introduce such a program, however, need to be accompanied by certain conditions. For one thing, employees have to accept such participation as legitimate.<sup>6</sup> If having such a say does not fit in with worker norms or culture or is not seen as a genuine attempt by management-labor teams to improve work, it is unlikely that participation will be effectively exercised.

Both management and the employees need to be educated about the effects of shift work on health-related conditions such as loss of appetite, fatigue, difficulty with sleep, and bowel problems. Unless this education takes place, employees may not always identify health and family-related problems with their shift work. They might instead think some of these problems are due to their spouse's cooking or the personalities of their

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\*For a history of shift work see Bjerner, Holm, & Swenssen (1948) and Mott, et al., 1965.

spouse and children (Mott et al, 1964, found such misperceptions very common).

Employer and employee could not be expected to be skilled in diagnosing the source of these problems without proper education. Decisions need to be made on the basis of such information and not merely because "Joe says 'nights are easy because they don't hassle you as much.'" The medical department of a large organization might, with the agreement of employees, perform diagnostic screening of persons who are not on straight day shifts to help provide the employee with information on whether or not the employee was the type of person who could or could not adapt successfully.

It is unlikely that unions will easily set aside the seniority system in favor of such procedures. On the other hand, it might be possible to set up a participatory system in which seniority took precedence whenever there was a conflict for certain work assignments.

*Rotating the Role Set Rather Than Fragments of It.* Shortly before coming to this conference I was talking with a woman who told me she had worked for three years on the night shift and then had been moved with two other women to the day shift. There, she and her old co-workers from the night shift pretty much kept to themselves and apart from the other day shift employees. Her new supervisor on the day shift told her that "Things are going to be different on days. You've been having it too easy on the night shift." The supervisor then proceeded to carefully clock the length of the coffee breaks for these women and criticize them when they took too long. The supervisor overlooked similar violations by the more seasoned day workers.

This story struck me because it parallels analyses of some survey data of police which suggests that some types of rotating shifts may indeed create interpersonal problems at work such as those mentioned by this woman.\* Data were gathered on 75 police from two precincts in a metropolitan area on the west coast of the United States. These police all completed questionnaires about various aspects of their work. These employees were either on fixed shifts or else were on rotating shifts — shifts which changed approximately every 20 to 180 days (the mean was 100 days). Consequently, this probably is the type of shift rotation period that allows most persons' circadian rhythms to adjust to phase-shifting. It cannot be assumed, however, that all the men kept the same waking hours during nonwork days.

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Before the data were examined to see whether or not men on the two shift patterns reported different levels of job stresses and strains, an inspection of their mean levels of education, age, and tenure was made to determine whether there were differences associated with selection into rotating versus the fixed shift. There were no differences in age (29.2 years, S. D. = 5.5) nor in education (14.5 years, S. D. = 1.1). Police on rotating shifts had slightly more seniority but the difference had no statistical significance in interpreting the following findings. The sample was restricted to day and swing shifts with no significant difference in the distribution of police by time of day. Significant differences by type of shift are presented in Table 1.

TABLE 1  
*Difference in Stress and Strain Among Police on Fixed Shifts  
and on Shifts Which Rotated Every 20-180 Days*

| Self-report measure                         | Shift Pattern |          | t     | d.f. | p =  |
|---|---------------|----------|-------|------|------|
|   | Fixed         | Rotating |       |      |      |
| <i>Stress</i>                               |               |          |       |      |      |
| Quantitative work load (9/.83) <sup>1</sup> | 3.3           | 3.7      | -3.28 | 73   | .002 |
| Role conflict (3/.80)                       | 1.5           | 1.9      | -2.76 | 74   | .007 |
| Underutilization (3/.85)                    | 2.0           | 2.3      | -1.45 | 74   | .150 |
| Social support: supervisor (4/.93)          | 3.1           | 2.8      | 1.71  | 74   | .091 |
| Social support: others at work (4/.76)      | 3.2           | 2.9      | 2.03  | 74   | .045 |
| Social support: nonwork (4/.87)             | 3.6           | 3.5      | .31   | 73   | .759 |
| <i>Strain</i>                               |               |          |       |      |      |
| Boredom (3/.86)                             | 1.4           | 1.8      | -2.03 | 74   | .045 |
| Dissatisfaction with work load (3/.82)      | 1.7           | 2.3      | -3.11 | 74   | .003 |
| Dissatisfaction with job (4/.85)            | 2.8           | 3.2      | -2.63 | 74   | .021 |
| Somatic Complaints (7/.76)                  | 1.2           | 1.3      | -2.39 | 74   | .019 |
| Anxiety (4/.75)                             | 1.5           | 1.6      | -1.01 | 75   | .318 |
| Depression (6/.83)                          | 1.5           | 1.6      | -.41  | 75   | .680 |
| Irritation (3/.80)                          | 1.8           | 2.0      | -1.29 | 75   | .203 |

*Note:* Data from two police precincts where age was unrelated to assignment to shift pattern. There were 50 persons fixed shifts and 26 on rotating.

<sup>1</sup>Numbers in parentheses indicate number of items in questionnaire index and estimated reliability ( $r_{kk}$ ; see formula G-18 in Nunally, 1967) respectively. Item content is present in Caplan, et al. (in press).

Compared to police on the fixed shifts, those on rotating shifts reported significantly higher levels of work load, role conflict, underutilization of skills and abilities, and lower levels of social support from supervisor and others at work. There were no differences in the amounts of such support from nonwork sources such as family and friends. The men on the rotating shifts also had the highest scores on boredom, on dissatisfaction with the work load, and on overall dissatisfaction with their jobs.

They also reported the most somatic complaints. Somatic complaints is an index with items such as "you had a loss of appetite," "you had trouble sleeping at night," "you were bothered by having an upset stomach or stomach ache," and "your hands trembled enough to bother you." There were nonsignificant tendencies for the levels of anxiety, depression and irritation to be higher among the police on rotating shifts.

These findings suggest some hypotheses that could be pursued in future research and also followed up in attempts to improve the lot of employees on rotating shifts. Much of the stress reported by the police on the rotating shifts appeared to be interpersonal in nature: role conflict, difficulties with the supervisor, and difficulties with other employees. In these instances it appears that only part of the employee's role set was being rotated. The "line" was being rotated every three to six months but the staff was not. Furthermore, not all of the line was necessarily rotated at the same time. This meant that the rotating men were essentially entering a new job with new bosses and co-workers at each rotation period. This could conceivably weaken the quality of relations among the men and their superiors and lead to role conflicts.

The overwork but underutilization of skills and abilities reported by these employees may have occurred because the supervisor did not get to know their abilities as well as the abilities of the men who remained on the same shift for a longer period of time.

With regard to the higher levels of psychological strain among the men on the rotating shifts, there are few explanations that follow directly from the data. Although most of the measures of job stress are unrelated to the strains in these shift work groups, social support from the superior and from others at work is associated with dissatisfaction with one's work load ( $r$ 's = .24 and .21 respectively,  $p$ 's < .05). When the scores on dissatisfaction with work load were residualized for the effects of the lower social support among the men on rotating shifts, the difference in dissatisfaction between those on fixed versus rotating shifts dropped (estimated variance,  $\omega^2$ , dropped from 10%,  $p = .0003$ , to 7%,  $p = .05$ ). This suggests that some of the dissatisfaction with the work load among the employees on the rotating shifts was related to the poor social relations they experienced with their supervisor and the other police.

The findings, of course, are not fully explainable because we lack data on the nature of all the work conditions in the police precincts comprising the sample. The men were rotated by request and by seniority within those requesting rotation. Consequently it is possible that the most dissatisfied persons rotated. The precincts, however, did not allow the police to remain on the same shift for more than nine consecutive months so that some persons were always rotated on the basis of how long they had been on a shift rather than on the basis of seniority and personal requests for a change of shift.

Despite the inability to fully interpret these shift work findings, the results are worth noting. The findings suggest that some of the effects on humans of rotating shifts may be due to psychological reactions to changes in the composition of the role set brought about by shifting people. These effects would appear to be independent of any role that physiological circadian rhythms might play in employee health.

To avoid such disruptions in the role set of persons on rotating shifts, it might be feasible to rotate entire role sets including supervisors. Such a procedure would avoid fractionating a work team that has learned to deal effectively with one another — and the result could be improved employee satisfaction, a maintenance of the continuity and quality of working relationships between supervisor and supervised, and a reduction in role conflicts.

Recommendations such as the preceding obviously must be tailored to fit the particular needs of the organization and its work force. Since seniority plays a major role in determining how people are assigned to shifts and patterns of shifts in many organizations, one might have to allow seniority to operate yet try to instill strong norms via union-management agreements in order to encourage employees to keep together as cohesive teams. In some types of organizations, it might be possible to hire people in cohorts where all members share the same seniority and can be rotated as a group.

### *Conclusion*

It is likely that future research on shift work will proceed along a variety of lines. Some of this research probably will appear esoteric to the practitioner and other forms of it may appear relevant. It may be very difficult to predict, however, from where the most productive findings will come because science often has a way of producing useful findings which are purely serendipitous. Nevertheless, I am impressed with and hope we will encourage the programmatic efforts of Dr. Akerstedt and his colleagues at the Laboratory for Clinical Stress Research because they have the advantage of interdisciplinary collaboration guided by an overriding model of stress and health. Perhaps this type of collaboration will become more widespread.

The final evaluation of our scientific contributions to society will be based on their eventual utility. That judgment, however, will need to be rendered at each particular site of application. The best proof of whether or not a particular system of shift work will be appropriate in a work organization likely will come from the particular experiences of that organization. Consequently, I hope that leaders in both labor and management embark on evaluative field trials as a complement to the more meticulous and sometimes more remote efforts of us as scientists.

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**SHIFT WORK AND HEALTH—  
INTERDISCIPLINARY ASPECTS:  
DISCUSSION II**

*Jon F. Sassin*

I should like to compliment Dr. Akerstedt on his paper, which was very clear and broad in its perspective and provided some direction. There are a number of points I should like to emphasize for later discussion, which were brought up both by his paper and by others today.

First, with respect to biological rhythms, I have a question: "Do biological rhythms such as those discussed today ever invert or truly shift?" I know of no evidence to answer this. If they do, how long does it take before reinversion would take just as long as the initial inversion of the cycle? This would lead us to look more closely at the evidence that rapid rotation of shifts is better than the permanent shift.

The second point that I want to make concerns the degree of resolution of the studies to be done. For example, in my own field, hormone and sleep interaction, studies of minute-to-minute changes in hormone concentrations revolutionized investigation. Perhaps in shift work, individual differences must be looked at more closely and small changes must be examined carefully. For example, one hour of sleep deprivation can be detected by using appropriate tests, so rather than looking at week-to-week or month-to-month changes, one might look at minute-to-minute changes in a productive way.

The third point is a problem of balance between two ways of looking at variables. One might take the Sutton's law approach, that is, going "where the money is." For example, the study of sleep in shift workers would be important because it is a common complaint and, in addition, we have a good handle from many years of sleep research. But there is the other side, manifested by the story of the man who saw his neighbor out feeling about on his lawn. When asked what he was doing, the neighbor said he was looking for the key to his car. The man said, "I will help you; show me about where you lost it." The neighbor replied that he had lost it in the basement of his house. "Then why are you looking out here on the lawn?" The man answered, "Because the light is

better out here.” While there is more “light” on sleep and a few other phenomena, perhaps we should be searching the dark for new variables to investigate.

Another problem is the problem of the laboratory *versus* the “real” environment, and the question of what is a “real” environment. In this respect, we are making value judgments about “good” and “bad” or “real” and “artificial,” and it is much like Robert Persig’s analysis in the book, *Zen and the Art of Motorcycle Maintenance* in which he actually becomes psychotic in an attempt to define “quality.”

What is “real” is very difficult to define and for many investigators, a shift to what is probably a “real” environment may require a 180-degree phase-shift in their own thinking. I feel that a move in the direction of field studies is now warranted. For example, what is the light-dark cycle of that weevil *inside the apple* versus being on a leaf? These kinds of questions can only be answered by going inside the apple. Similarly, what is sleep need as measured in a lab as compared with a subject’s real life sleep need where motivations are quite different?

That brings me to another point, and that is the word, “motivation.” I have not heard it spoken yet today. It is probable, however, that motivation is a most important factor in the selection and adaptation of a person to shift work. Motivation is known to overcome a variety of negative factors, such as the effects of sleep deprivation. A person may be sleep-deprived for several hundred hours consecutively and still be able to overcome fatigue and tiredness if he is motivated enough. This may help explain differences in results between studies of essentially the same phenomenon.

A motivating factor, social gain, has been mentioned, e.g., families staying together because the husband goes on shift work, as seen in Navy studies indicating that many Navy families stay together only because the husband goes to sea. If he were home there would be a divorce within several months.

Finally, there is need for cooperation in all of these studies on the part of industries that are involved. As investigators, we either have the cooperation of industry or use a captive population such as military or medical personnel, nurses and doctors. In getting the cooperation of these industries, investigators will need the help of federal agencies.

## THE ECONOMICS OF SHIFT WORK AND ABSENTEEISM

*John D. Owen*

My perspective on shift work is influenced by my work on a large-scale study which I have just completed on the future of what are called Alternative Work Schedules — i.e., alternatives to the standard 8:30-5:00, Monday to Friday schedule. Under this heading, I have been studying such future alternatives as the 30-hour workweek and flexible hours schemes that afford the individual more choice in the scheduling of his working times. The conclusion of that study is that we are very likely going to be following the new European practices, and will offer a large proportion of the workforce, perhaps even the majority, the “flexitime” system. It also is possible, though not as likely, that we will simultaneously reduce hours of work and so give leisure-time and family activities the dominant position in the time budget now held by working and commuting times.

However, any such optimistic forecast of greater emphasis on individual needs in the scheduling of the timing, and, possibly, the number of hours worked per week, must confront the fact that the practice of shift work continues; in fact, it is quite widespread and may be expanding. I recently have been able to obtain some data which measure the current extent of shift work. For many years, the U.S. Department of Labor has been asking, at regular intervals, random samples of employed Americans how many hours they work per week. But in May, 1973, the question list was expanded, and individuals also were asked to give the times at which they regularly began and ended work. If one defines shift workers as those employees whose regular eight-hour day is not limited to the 7 a.m. - 6 p.m. time span, these data show that about one-out-of-six full-time, non-agricultural wage and salary earners are on shift work. Among blue collar employees in manufacturing and mining, over one-fourth are on shift work. Among male employees in this occupational-industrial category, the shift work rate is about three in ten. Somewhat similar results are obtained from the area surveys of the Department of Labor: the proportion of manufacturing workers on second or third shifts varies from 10.5% in Miami to 43.2% in Detroit.

Widespread use of evening and night shifts is, of course, a common phenomenon throughout the industrialized world. It recently has obtained more attention in Northwest Europe, possibly because a larger proportion of the non-agricultural workforce there is in the secondary industry, manufacturing, where shift work is more common while the tertiary service industries are further developed in the U.S.

Some European estimates of the growth of shift work were presented at a conference on "What Americans Can Learn from European Work Scheduling Practices" (which I held in Venice last Fall as part of my investigation of scheduling practices); this study, based upon data compiled by trade unions affiliated with the Organization for Economic Cooperation and Development (OECD), estimated that shift work has doubled in the past 10 years in Northwest Europe. I should point out that management and government representatives at our conference sharply disagreed with the 100%-increase estimate, although they conceded that a significant rise in shift work had probably taken place.

The persistence of shift work implies an important qualification for my optimistic forecast that personal choice in work schedules will be expanded. True, some workers prefer evening or night work, but the prevalent practice of paying a money differential to shift workers is a signal to the economist that the supply of workers who would want non-standard hours for their own sake — i.e., in the absence of a financial inducement — is very probably less than the demand of industrial employers for workers to put in these hours.

However, before simply dismissing shift work as a social ill — to be decried or even outlawed along with such other relics of 19th Century individualism as child labor or the 14-hour day — let us consider some of the positive contributions it provides: Shift work has two broad social functions. It meets the needs of people for services in the evening or nighttime, and it economizes on physical capital stock by utilizing it more fully.

The list of services provided in off-hours is large and growing: every night, an army of police and security guards now endeavors to protect people and property against crimes. Firemen must be available 24 hours a day. Doctors, nurses, and hospital staff are similarly available to provide emergency medical care at all hours.

Of course, not all off-hour services are of an emergency nature. The proportion of Gross National Product allocated to recreation has more than doubled in the post World War II period and, as a result, an ever larger number of people are required to work while others take their leisure. Restaurant workers must also work during normal leisure hours. In addition, the rising proportion of two-earner families generates an increasing demand for late closing hours for retail outlets, to accommodate the shopping needs of the working woman.

The other basic function of shift work is the more traditional one — to make maximum effective use of physical capital equipment in manufacturing, mining, the transportation of goods, computer operations, and so on. In each case, the opportunity cost to the employer of keeping his capital stock idle outweighs the additional labor costs that a second or third shift would require.

In general, shift work can be expected in continuous process industries and in industries which are capital-intensive, i.e., where the capital to labor ratio is high. However, it is not just the amount of capital in place that is important in this calculation, but the rate at which it is effectively used up. In a recent paper, Bernard and Ghanadjian argued that the critical factor in the increase in European shift work has been the increasing rate of obsolescence of equipment, as the Europeans modernize their industrial plant.

Of course, the benefits of shift work are not confined to those received by the employer or his employees. Gross national product is larger than it would be otherwise and so the tax base is larger. This provides potential benefits to the rest of the citizenry.

Shift work may come to play a particularly important role in the United States in the next few years, insofar as it helps us to cope with the shortage of physical capital, which many experts predict.

Europeans see additional reasons for shift work. The Polish economist, Kabaj, views it as a way of generating more employment opportunities in the capital-intensive sector of the economy. The Finnish economist, Kohi, argues that shift work facilitates fully automatic production processes, and that this, in turn, eliminates the need for many boring or unpleasant jobs now required by processes that are only semi-automatic. Hence, there are many social and economic advantages of shift work.

Against all these advantages, one must place the personal or family dislocation caused by shift work, and its possibly negative effects on health. These employee costs are translated into employer costs when a higher rate of absences occurs on shift work — through illness, or because the non-standard schedule induces healthy workers to take time off to meet family and recreation needs or for some other reasons.

The statistical evidence of a positive relationship between absence and shift work is quite mixed. It consists of fragmentary studies and is based largely on foreign data. It tends to be unsophisticated in its use of econometric or sociometric models. At this point, the available evidence could be interpreted as giving very weak support to the hypothesis that shift work increases neither absence nor illness rates. At least the evidence to the contrary would not be strong enough to reject a null hypothesis that there is no such relationship.

In my view, for an adequate test of this hypothesis, one needs both a satisfactory data base and a meaningful empirical model. The data base should meet three simple conditions:

- (1) Because of possible international differences, American data are preferable to foreign data for the purpose of making inferences about American conditions.
- (2) Because of possible differences among regions, and probably differences among industries and occupations, data from a national, random sample would permit broader generalizations than would data from, say, a single plant.
- (3) Data should report illness absences separately from other absences. Since employees have an incentive to report absences to their employers as illnesses, I would guess that data collected independently (perhaps in the privacy of the worker's home) would be preferable to data obtained from employer records.

None of the various studies of shift work absence have had a data base that met all of these three basic conditions.

When a suitable data base is available, it still is necessary to design an empirical model that will look at the contribution of shift work to sickness and other absences in a theoretical framework that considers all the important sources of absenteeism. Otherwise, a simple correlation between shift work and absences could be misinterpreted as meaning that shift work itself is the cause of higher absence rates, when this is not the case. An adequate model should take into account three sources of variation in absenteeism, apart from work scheduling:

- (1) Individual employee characteristics: such personal characteristics as age, sex, race, job experience, education, wage rate and number of dependents are just some of the variables that might be expected to influence absenteeism. For example, one hypothesis which I have found useful in explaining absences is that those workers who would prefer a shorter workweek, but who take full-time work because of the generally better employment opportunities open to full-timers, are more likely to be absentees. Those who would prefer longer hours, to obtain higher weekly earnings, would be less likely to be absentees.
- (2) The nature of the job or industry insofar as it influences employee behavior. Work that is unpleasant, physically demanding, low in status, and does not offer training or promotional opportunities might be expected to produce more absenteeism than other work.
- (3) The nature of the job or industry insofar as it influences employer behavior. Where absence causes severe economic dislocation, employers are likely to have a stricter code for penalizing the absentee. They also will endeavor to select employees expected to be less prone to absenteeism.

I have made some progress with developing and testing a model of absences, using the same Department of Labor survey data for May, 1973 that I described earlier. (These survey results do meet my three basic criteria for a data base.) I am encouraging a student of mine, Gerald Goldberg, to develop this work into a doctoral dissertation, under my supervision. So far, we have found a definite negative relationship between the number of hours a worker is "expected" to work and his absence rate. My methodology here was to obtain "expected" hours by regressing the weekly hours of work of all wage and salary workers, including part-timers, against a vector of personal characteristics (similar to the list I cited above). Then, the regression coefficients obtained in this fashion were used to estimate the expected number of hours of each full-time worker.

Finally, the absenteeism rate of those who are expected to want to work less than the standard workweek of 40 hours was compared to the rate of those who are expected to want to work 40 or more hours. This technique does bring out some important differences in the absentee behavior of different types of workers. On the average, the absence rates of those expected to want to work less-than-full-time (but who are, in fact, working full-time) were significantly higher than the rates among those expected to want full-time employment.

Mr. Goldberg and I have not yet carried out tests for the various effects of industry and occupation, but the preliminary crosstabs that we have constructed suggest that this also will be a promising source of results.

As our understanding of the phenomenon of absenteeism is improved, it will become possible to measure the net effect of shift work in exacerbating or ameliorating it. I am not yet quite ready to carry out this shift work analysis (I first must study the effects of industry and job on absences more clearly). However, some preliminary work which I have done in preparation for this conference appears to offer some very promising results.

Among males, illness rates appear to be consistently higher among shift workers, although the relationship between shift work and illness appears to be somewhat weaker among females. These results give some tentative support to the hypothesis that absences, or, at least illness absences, are more frequent among shift workers. However, much more empirical work is needed before I can attach any great confidence to this set of results.

In conclusion, if shift work is to remain as an important institution in American society — and this seems very likely indeed — we must know more about its effects on physical health, and on mental and psychological well-being. The analysis of absence data is only one step in that direction, but in my view it is a most important step.

## **METHODOLOGICAL PITFALLS OF SHIFT WORK RESEARCH: DISCUSSION**

*Donald I. Tepas*

The proceedings of this symposium clearly reaffirm what I suspect is the unanimous *feeling* of professionals working on this problem and in related areas: The workweek and shift schedule of a worker do affect him.

Affirmation of this belief is expressed directly and indirectly as a result of a wide ranging variety of field and laboratory studies. We can agree on this position, and we should not overlook this important fact: We have progressed to the point that we no longer need to argue *if* workweek and shift schedule are significant variables.

As I see it, we have now progressed to another level of scientific development. It is clear that the interaction of workweek and shift schedule factors with the behavior and environment of the worker is not a simple interaction. And the relationship of shift work to health is not a simple relationship. Having justified fully the importance of workweek and shift schedule factors, we are now beginning to enjoy the freedom of this sophistication. We can acknowledge that many studies are of poor quality. We can note huge gaps in our knowledge. We can admit the limitations of many of our traditional tools of investigation. We can look for positive as well as negative effects. Complex multiple-variable laboratory-field projects can be contemplated with a sense of reality rather than fantasy.

### *Problem*

Appropriately, this level of sophistication has been clearly evident in the presentations and discussions of this symposium. Statements of problems which should be explored, questions which should be asked, and expressions of willingness to explore practical applied problems abounded. This is fine, but I am concerned that our enthusiasm for this area not overlook this fact: Many of the problems and issues which we are now addressing were significant impediments to obtaining widespread acceptance of the notion that workweek and shift variables are significant health factors worthy of research. In many cases, the problems we are proposing to investigate today are related to the same variables which

previously were cited by critics of shift work effects as artifacts producing spurious shift differences.

If we are to concern others with the importance of shift and work-week factors, we must make an extraordinary effort to show that we are sensitive to potential artifacts and make a conscious effort to control or monitor related methodological problems. At this point in the development of the area, it is very important that we clearly demonstrate our sophistication. This not only should be done by the obvious investigation of new and perhaps more complex problems but also by overt manifestations of methodological sensitivity and skill.

In addition, proper problem selection is extremely important. We should select problems for study which match, but do not greatly exceed, our current ability to do research in the area *and* comprehend the results. In sum, vigilant artifact control and discriminative problem selection are high priority items.

#### *Pitfalls*

I should like to rephrase many of the issues and problems discussed by other participants in this symposium. In this case, I shall phrase them as methodological *artifacts* which must be considered, controlled and studied. The varieties of research artifacts in the shift work area are not significantly different from those common to most behavioral and health research. They usually are discussed in research methods texts in a variety of forms.

Commonly, these potential artifacts are classified into a finite number of overlapping classes, the number of which varies from author to author. I should like to group them in an order and form which is appropriate for the shift work research area. In each case, I shall attempt to relate the category to a dimension of shift work research. The categories are neither independent nor exhaustive, but they are clearly related to the problems of contemporary shift work research.

#### *Real-Time Events*

In computer terminology one uses the term "real-time" to refer to the processing of information as it is received, at a rate which makes the processed information available for influencing the event being measured and controlled. We must not forget that human research is always a real-time process conducted in a social and cultural environment. Contemporary shift work research is beginning to recognize this. Research must not limit itself to on-the-job production, efficiency and safety but it must also show a concern for off-the-job worker performance, satisfaction and health. The *complete* and *final* understanding of shift work and workweek problems does require the study of both on-the-job and off-the-job factors, but we are nowhere near that point in development of our knowledge base in this area. We should not feel a compulsion to study

*all* sources of variance. We must exercise care to assure that those off-the-job events or factors we study have major and important on-the-job effects.

Obviously, there are some off-the-job events which, under unusual or infrequent conditions, probably can affect worker job performance. Many of these off-the-job factors can produce major artifacts but only deserve minor attention as potential independent variables for contemporary shift work research. Let us take an extreme and simple example: The assassination of a President of the United States. I would assume that such an event could result in significant short-term changes in production, accident and absentee rates. Differential shift effects might be produced depending upon the time and nature of the assassination. As I see it, the study of shift work effects produced by this or other unusual events is not of high priority given our contemporary state of knowledge. Contemporary research must guard against the possibility that such an event could significantly distort the findings of shift work research.

Perhaps a somewhat less obvious example is in order. Eating habits may or may not interact with shift work activity. While this may be a problem worthy of study, a cautious approach to this class of variables is more appropriate. East European autoworkers breakfast on hot soup. Many West German autoworkers breakfast on their version of the hot dog. Southern U.S. autoworkers may breakfast on grits while a Detroit autoworker enjoys the currently-popular sugar-coated cereal. Breakfast diets vary among and within cultures. They can also vary with time, particularly in the U.S., depending on the activity of food manufacturers and their advertising representatives. It seems reasonable to suggest that one should not give high priority to contemporary study of the effects of sugar-coated cereal on shift work; however we cannot ignore the possibility that gross differences in breakfast menu may override shift work variables. Dietary controls, or lack of them, must be considered in the design and evaluation of shift research.

#### *The Hawthorne Effect*

Named after a classic study of female industrial workers, the Hawthorne Effect refers to situations in which *any* change in conditions results in increased production.<sup>3</sup> Although usually interpreted to be the result of high morale in workers due to increased interest in them, a variety of interpretations or causes are possible for this phenomenon. Since it has been demonstrated in a population of industrial workers, we must pay attention to this possible artifact in any study of industrial shift or work-week change. I suggest that this currently may be a special problem, since shift work rarely has been studied in depth and popular interest is relatively high.

In selecting populations for study under conditions in which funds available nationally are limited and the range of project must be restricted, there is the distinct temptation to select either un-studied industrial workers or populations having severe labor-management problems. In the former case, it seems reasonable to suggest that the Hawthorne Effect is most likely to manifest itself.

In the latter case, one might even expect a "Negative Hawthorne Effect." That is, *any* change in conditions might result in decreased production! Given an objective of obtaining generalizable findings about positive and negative shift work conditions, there would seem to be little value in a demonstration of either of these effects. On the other hand, proper control of this complex variable probably calls for sampling a variety of locations, managements and unions. It is quite possible that the study of common and stable industrial populations may be more productive of significant findings than studies aimed at the evaluation of crisis situations.

#### *Investigator Expectations*

Given the fact that by far the majority of research investigators are responsible and objective scientists, it is nevertheless appropriate to note that studies tend to produce results compatible with the expectations of the investigator. Sometimes referred to as "Pygmalion-like" effects, wishful thinking by investigators may result in subtle or overt variable selection as well as manipulation which seriously distorts findings. The corporate sponsorship of most shift work studies in the past suggests conditions which promote biasing effects. Many of these studies have attempted to evaluate shift work effects through existing corporate records of production output, work absence, accident rates and related industrial data. Can we consider this information as a fully bias-free data base?

Given employer study support as well as the use of employer defined and collected raw data, one must consider the employer as an investigator to some degree. It is very difficult, under these conditions, to think of the resulting data as clearly unconfounded data free of any investigator influence. It is not surprising that many of these corporate studies report no shift effects and in some cases shift work benefits which clearly are not compatible with laboratory research expectations. Indeed, one must remember that the demonstration of negative shift work effects on health probably would result in major revisions of corporate shift work bonus schedules.

As an alternative to this, many contemporary investigators are beginning to turn to union sponsorship of studies. Selecting workers for study through unions has a number of advantages, some of which will be discussed later, but it must be remembered that many of the same cautions must be observed: The union-as-investigator may result in a confounded data base.

I do not mean to suggest that union-sponsored or corporate-sponsored research need always be biased. What I am suggesting is that a great deal of care must be exercised in conducting and reviewing data collected with such controlling sponsorship to prevent the erroneous acceptance or rejection of shift work and workweek hypotheses. It would appear that the National Institute for Occupational Safety and Health has a unique charge and challenge, since it is faced with the possibility of minimizing artifact produced findings by providing investigators with research support not tied to labor or management. One would hope that management and labor appreciate the value of fair and un-biased evaluations, and that they acknowledge this by providing government-sponsored investigators with access to their facilities and workers.

#### *Subject Bias*

The Hawthorne Effect, discussed earlier, can be viewed as a form of subject bias. One can consider Hawthorne type effects simply as a manifestation of workers trying to provide investigators with the effects the investigators want. A similar and perhaps frequently-related subject bias can occur in research using volunteer subjects. Rosenthal and Rosnow<sup>4</sup> have demonstrated quite well a "Volunteer Effect": The age, education, intelligence and personality of persons who volunteer for laboratory and field studies are not representative of people at large. It would seem reasonable to paraphrase this and say: Workers who volunteer for a research study are not representative of any group of workers in that industry or job classification.

With regard to shift work, the problem becomes even more complicated. Long-term shift workers may, in fact or in practice, be volunteers for a shift which they prefer and/or tolerate. Thus, there may be a self-selection process of sorts which may tell us more about who can do shift work than what shift work does to people. It is quite possible that shift effects have been masked in some studies because the worker sample includes mainly those who have successfully adjusted to their schedule, hiding workers with adjustment problems who are in a minority or have ended their employment.

One way of avoiding this artifact can be the satisfactory use of contemporary sampling techniques to obtain appropriate representative samples. This, of course, frequently requires the cooperation of most of those in the sample population if the technique is to remain in order and be valid. One could argue that corporate-sponsored or union-sponsored research are approaches more likely to achieve the required sampling criteria. In practice, I doubt that this is true. For example, union-sponsored-and-run medical testing programs have reported disappointing levels of member participation. Proper concern in society with the invasion of personal privacy also makes required research participation by workers

improbable and probably will limit the future use of personalized data banks for long-term study of individual workers. One technique which has not been extensively used is the payment of a *significant* honorarium to workers providing data to researchers. While this might minimize Volunteer Effect to a considerable degree, caution would be called for that some sort of "Honorarium Effect" not develop. In any case, the worker honorarium approach appears to deserve further test.

In sampling workers, the tendency has been to study particular plants or industries. There is reasonable evidence to suggest that workers should be sampled on the basis of the type and quantity of work performed rather than on the basis of industry or plant.

Sedentary workers, for example, probably adjust to shift factors more quickly than heavy manual workers.<sup>2</sup> Given all of the controls which future shift work will call for (age, sex, work history, etc.) if comparison groups are to be matched, it seems reasonable to suggest that there will be too few workers available for study in a particular job classification within a specific plant (and perhaps industry) to discern any significant differences between matched groups.

This suggests a positive advantage for research working through unions, since matched worker groups of adequate size might be gathered by selecting subjects across plant and industry lines by using job classification as a grouping. This approach has some obvious problems, too, but may be the only practical solution to worker sampling problems as the sophistication of research in shiftwork continues to develop. Thus, we may have to consider the feasibility and problems associated with multiple-source sampling of shift workers.

#### *Sleeper Effects*

As we have already noted, self-selection of work schedules by industrial workers may mask some of the problems induced by shift work. Van Loon,<sup>7</sup> Weitzman<sup>10</sup> and others have clearly demonstrated the immediate effects of some acute changes in work schedule. It is also clear that for short periods of time most individuals can tolerate extreme deviations in work-rest schedule.<sup>6</sup> Halberg and Haus noted earlier in this symposium that animal research indicates that long-term exposure to certain work schedules may decrease life expectancy. One might term such an effect, and other effects which take a long time to manifest themselves, Sleeper Effects: treatment effects which appear in subjects only after the passage of a relatively long period of time. Obviously, it would be easy to conclude that a particular worker population was completely healthy and unaffected by the administration of a particular treatment if the period of observation was limited to a point in time prior to the manifestation of a major effect.

From studies of workers, there is little evidence in support of a delayed manifestation of health problems in shift workers. This is perhaps

related to two factors: little relevant data, and possible artifacts due to corporate sponsorship. I suggest that we cannot rule out the possibility of Sleeper Effects and that care must be exercised to insure that we do not overlook this possibility. I expect that most industrial toxicologists would readily predict shift-related Sleeper Effects simply on the basis of their general work with toxic substances. The National Institutes of Health, having the power to fund long-term studies, provides an opportunity for the longitudinal study of shift workers. Such research may identify significant Sleeper Effects of a sort never observed in relatively short termed studies financed by industry. Related to this, it should be noted that the relatively high rate of job changing in our society also suggests that longitudinal study of industrial workers cannot be linked to employment by a single corporation. It may be a fact that cross-sectional studies are a more appropriate approach to revealing Sleeper Effects, due to problems associated with real-time event artifacts and personal privacy issues.

#### *Single Source Silliness*

During the 1920s and 1930s, behavioral scientists spent a lot of time attempting to develop *the* best methodological approach to their subject matter, attempting to design *the* definitive experiment, and searching for *the* discriminating measure. If we have learned anything in the subsequent years of research, it is that such single source silliness must end. Acceptance of a single source of data as a definitive indicant simply increases the probability that artifact will be promoted as fact. And acceptance of artifact as fact results in spurious applications, research and teaching.

Solid facts for safe applications are produced by generalization across data gathered by using quite different methods, by families of experiments, and/or by the measurement of multiple variables from various domains or levels of study. Given the current demands and values of our society, it is tempting to overlook this lesson of the past in search for short-cuts to the solution of pressing problems. Humans are complex organisms placed in a complex environment, and spectacular single source findings should always be approached with question rather than heralded as break throughs.

The need for multiple source data in the shift work/health area is perhaps best noted when it comes to a discussion of field versus laboratory research. At our present state of technological development, most field data involve the use of paper, pencil and questionnaire, whereas most laboratory research involves tightly controlled experimentation using specialized equipment. One can argue the overall importance of field versus laboratory research and assign a higher priority to one of them. It seems clear to me, however, that the two approaches complement each

other quite well and that investigations using both methodological approaches are *required*, given our current state of ignorance.

Taking an extreme example, I note that a worker could be suffering from a terminal disease without this ever showing up on any present-day field questionnaire if the worker himself were not aware of the results of a particular laboratory test. In a similar manner, many individuals think they have a terminal disease and are shown to be in error only when laboratory tests are conducted. One cannot deny that field survey and questionnaire data have limits.

On the other hand, it also is quite appropriate to point out that the laboratory study of shift work frequently cannot proceed in a meaningful manner without some guidance from survey or questionnaire data. For example, if we wish to study workers with long-time experience at shift work, we have no realistic data with which to establish criteria for what is to be considered "long." There is no survey data which would tell us how long the average industrial shift worker with a particular job classification in a given industry has been on shift work. Among other things, it is clear that field survey data is required if laboratory research is to involve the use of matched representative worker groups. The research of Webb and his associates<sup>10</sup> on long and short sleepers provide a good, concrete example of the use of questionnaire, test and laboratory polygraphic study in a complementary manner.

The value of a *series* of parametric interrelated laboratory studies of workers has been demonstrated admirably by Colquhoun, both at this symposium and in his extended research program (1971). His research provides an excellent factual response to the critics of laboratory research on workers, and it points out very well the need for systematic parametric studies of workers. Some laboratory research on shift workers has a number of characteristics which do deserve additional discussion at this point. If we exclude studies of hospital staff, military personnel and college students, it must be noted that there are few if any laboratory studies of American industrial shift workers to be found in the literature. This would seem to be a very important gap in our knowledge. It is also noted that most of the human shift work effects demonstrated or suggested by laboratory studies of man involve short-term and acute exposure to new or different shifts. Are there long-term effects detectable in the laboratory?

Finally, it is noted that the customary design for human laboratory shift work study involves location of the worker in the laboratory for both the work and the rest aspects of the study. Little in the way of testing in the laboratory has involved testing industrial worker performance and sleep following usual work in its regular industrial environment.

I should like to argue that we not only need more laboratory research on shift workers but also that laboratory research on shift workers can

be conducted in a multiplicity of ways, many of which have not as yet been explored in any real sense. The laboratory study of experienced shift workers, from a wide range of job classifications and following usual daily employment, is now feasible with the techniques and methods already available. What is needed is encouragement and support of the sort which makes involvement with worker populations easier and more rewarding for both workers and experimenters.

The importance of physiological and behavioral measurement in the assessment of shift work already has been pointed out and provides a good example of the value of multiple measurement in this research. A fairly concrete example can be shown in our data from a study of subjects isolated in an experimental chamber for 48-hour periods while subjected to various work-rest schedules (Tepas, 1967). Figure 1 presents data

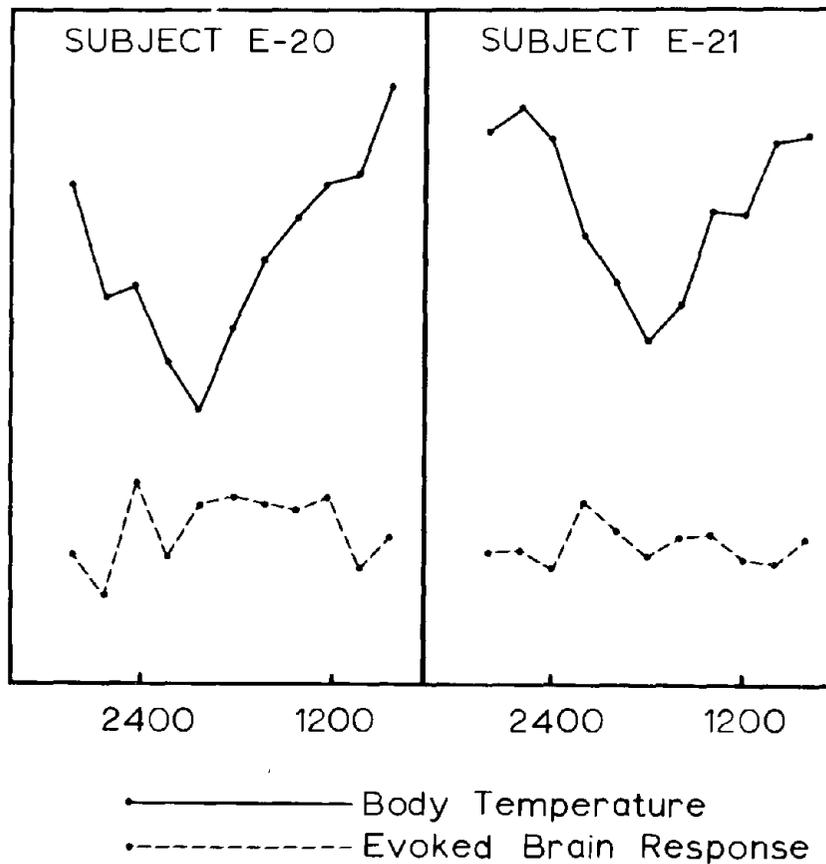


Figure 1. Methodological pitfalls of shift work research.

from two subjects administered a regular one-hour-work/one-hour-rest schedule. Both of these subjects demonstrate well-defined circadian variation in their body temperature data as easily can be seen in this figure. Concomitant evoked brain response (EBR) data do not demonstrate any obvious circadian variation in these two subjects, as can also be seen in this figure. The EBR data do correlate significantly with reaction times to an alarm tone signaling the start of work periods, whereas the body temperature and heart rate data do not. Body temperature did, however, interact with simple reaction time data collected *during* work periods, whereas EBR data did not. These data support Colquhoun's' argument that we cannot take body temperature as a simple invariant index of arousal or performance. In a sense, they also go a step beyond this in that they demonstrate that behavior-physiology-circadian relationships must specify the behavior and the physiological measurement involved. Just as there is not *a* physiological measure of the health status of the worker which "tells-all," there is not *a* behavioral measure of the performance status of the worker, and there certainly is not *a* single or simple relationship between physiological measures and behavioral measures. If a true picture of shift work/health interactions is to be obtained, it seems multiple source measurements are required.

### *Summary*

It is clear that experts working in a wide range of disciplines now agree that shift work is a significant factor influencing the health of workers. This position is based upon a large number of fairly basic research studies reported by a variety of investigators.

More sophisticated research directly examining shift work effects in American industrial workers is now appropriate and practical. In conducting this research, investigators must be vigilant in their effort to prevent a variety of artifacts from producing erroneous conclusions. The Hawthorne Effect, investigator expectations, subject bias, and late-occurring sleeper effects are all classes of artifact which must be controlled.

Given our current state of knowledge about shift work effects in man, study of unique and unusual phenomena must be approached with caution since spurious results may be produced by unidentified or unimportant variables serving as artifact producers. Also, recommendations or conclusions based on a single source of information should be avoided since they increase the probability that artifact will be promoted as fact.

At best, we should expect contemporary research on shift work and health to result in some general principles which can be applied across time and industry with reasonable confidence.

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**Session II**  
**Interdisciplinary Meetings**



### **Topic: Is Shift Work a Significant Health and Safety Problem?**

*This symposium was organized on the presumption that shift work leads to significant health and safety problems and that interdisciplinary efforts are essential in obtaining the necessary research in this area.*

### **Guidance**

The groups should involve discussions and development of *answers* to *these questions*:

- 1) What do we believe are the health and safety consequences of shift work?
- 2) On what knowledge are those judgments based?
- 3) How can we best research the health and safety consequences of shift work?

Listen and discuss. This is an opportunity to see the problems of shift work and shift work research from beyond the horizons of one discipline. Emphasize the unique causal and outcome dimensions your area of specialization contributes to understanding the consequences of shift work.

Present the physiological, psychological, social, medical and job-related dimensions believed to be essential for an effective interdisciplinary research program and discuss problems in measuring these dimensions.

Consider factors which have confounded prior research efforts. Discuss shift systems, type of work, and individual differences in work history and in sleeping, eating, and family and social patterns. Explore the importance of each of these variables in the health and safety problems of shift work and, therefore, in shift work research.

Describe physiological, psychological and medical individual differences which might *predict* poor shift adjustment or good shift adjustment. Consider what sleeping, eating, socializing, family, and shifting patterns may contribute to minimizing the health and safety consequences of shift work.

Each small group chairman or his designates will present a brief summary of his group's session to all the participants. There will be some time for questions or comments following each presentation.

### **Group I**

*Dr. Weitzman:* We had a small but select panel of eight. I should like to give the backgrounds of the participants since they obviously determined, to some extent, the direction of the discussion. We had five psychologists. One was interested but had not done work in areas of sleep and shift work or psychological relationships to rhythm problems. An-

other psychologist is affiliated with the Air Force and is interested in the problems of shift work in relationship to vigilance in monitoring function, ground base situations. Others were: a student going for a Master's Degree, interested in drug studies, animal and man's 24-hour functions; a physiological psychologist who was actively involved in a broad program on 24-hour measurements and relationships to shift work problems; a plant layout and safety inspector whose job it is to go around to plants and see if they're conforming to certain safety codes for the workers; an industrial hygiene engineer who is with NIOSH; another psychologist who is very actively involved in issues of performance and vigilance and myself.

Discussion was the first topic — the issue of what we were to do, what we wanted to end up with in this short period.

We thought it might be worthwhile to ask: suppose we had unlimited money, unlimited resources, and unlimited intelligence, but very limited knowledge? Then, what kind of an interdisciplinary program would we put together in the hope of ending with a relevant set of information to advise industry, workers in industry, and, possibly, community and social groups as to what are the important issues in a shift work problem in relation to the health and safety needs of workers?

The first thing we had to decide was what are the questions to be answered and what do we know. It turned out that we asked many more questions than we had answers for. We debated next if we should do all the work in the field or whether we should do it in the laboratory or if we should do both. Obviously, we concluded that we should do both. That is, we should move in and out of the laboratory to the field and the field to the laboratory with this broad spectrum interdisciplinary group.

What should we do in the field? What information should we gather? What research should be done, what experimental studies? Obviously, since man's capacity to make observations is unlimited and his ability to spend money to make observations is unlimited, we have to come up with focused hypothesis-based questions, or at least some explicit bias that may exist in us. What are the biases that we have, or hypotheses, if you want to use the scientific term?

We felt that the issue is, what does exist, what are the actual shift programs that do exist? Not what we think exists or what we'd like to mimic in a laboratory; but the important thing is what actually does exist?

There was unanimous opinion that a very thorough multi-industry program should be undertaken to find out what actually exists — not only what are the shift work patterns that exist but the consequences of these shift work patterns in terms of performance and health and safety

needs. We recognized that it would be very difficult to find out what people do and the consequences of what they do. It would be important, nevertheless, because there may be non-problems that we are trying to solve. It's important to solve this problem because, for instance, the preclusion may be that workers on a rotating shift are going to have all these dangerous things happen to them but, if one could find out, it could be that there are no dangerous things that happen; everything's fine and everybody's happy. I don't think that's going to be the case in a lot of situations, but we should find out.

The next area is where do we go to get that information. Obviously, we get it from as many different sources as we can. We felt that we have to get it from management itself, if they are willing to tell us the truth about what really does happen, when accidents do occur, what are their problems, etc. We want to get it from the workers directly on how they view their problems, how the problems affect them, etc.

And we need information on the relationship to the family and the social community relationship, small town vs. big city. In a one industry town where everybody's on shift work vs. a big city where maybe there are only 5% or so of people on shift work, what are the consequences to the workers, the availability of entertainment, etc., to the workers, and so on.

Consequences of shift work to health in relationship to age, we felt, also is an important question.

It was very difficult to determine — and we tended to avoid discussing — what are the important measurements of well-being or health or safety or performance. Some of us felt that “well-being” was a pretty good general concept though difficult to define, especially when it often happens that people say things like: “We don't care if he's sleepy or if he's not functioning well as long as he doesn't injure himself on the job.” Or “If he's performing 20 outputs per hour versus ten, that's perfectly all right; I don't care if he's sleepy or tired or has an ulcer next month.” These all are important in the whole general concept of well-being. It's too complicated to go into in so short a period of time, but, generally, we felt that well-being should be a very broad conceptual point of view.

In addition to these kinds of survey information gathering issues, we thought it would be very important to do measurements — longitudinal, to some extent cross-sectional, but longitudinal — measurements of people working in shift situations.

What kinds of measurements should be made? There is no question that one could almost indefinitely measure everything; and, indeed, every-

thing is rhythmic if you measure it. What are the important things to measure? What are the things that look as if they're going to have relevance to what we know now?

The great emphasis in our discussion was on the psychological and, in the broadest sense, mental performance functioning of the human being. It was not generally physical muscle contraction rates — not that they couldn't be important, but they are not very important per se. It's how the brain or the mind tells the muscles what to do and in what manner and sequence to do it that we felt was important. Therefore, we need measures of performance, measures of vigilance, within the field situation.

Now, how do you get that? One way, of course, is to measure how efficient the workers are. In other words, the night people can turn out only 20 items and the day people turn out 40 items, etc. Generally, this wasn't considered to be very useful and we've talked about the possibility of developing in task defined vigilance such as one of the panelists suggested in which, in the middle of doing some job, a task suddenly appears and the person has to do something to respond, like push a button or turn a light off, or has to maybe track something in the middle of some other task which has some significant relevance to the task at issue.

For example, a radar tracking operator might also be asked suddenly to look over there and follow a dot moving and push a button for 30 seconds. And that could be imposed immediately in the work situation and might even be a good measure of his functioning in a more quantitative, precise way. The other aspect, of course, is the whole 24-hour rhythmic function of this person. One suggestion was that there should be some definition of his 24-hour state, his phase map so to speak, and the technique of oral rhythmometry was mentioned. In discussion, it was generally felt that, in a select population of workers, this would be worth while as the indication of phase as well as amplitude, etc., over a longitudinal period of time in a working situation within a shift situation.

One point which I should make now is about the type of job. The significance of the job has to be related to the measurements you make. It's silly to do a careful tracking study on a night watchman who, every two hours, has to get up, walk around the plant, push a button, then sit down for two more hours. It doesn't matter that he has to have a very careful tracking job, for the person must be very vigilant. The same thing is true in relation to the kind of shift. If an industry never shifts less than a month at a time, and would never do so for certain constraints of that industry, it's silly to be concerned with a two-day shift, for example.

I think one has to start thinking in terms of relevance of the type of job, the industry, to that situation. This was generally agreed and

this was a focus of the work. Measurements within the ongoing situation, like definition of sleep-wake function, are important. There are portable technical devices (I think a number of us are using them) that are available to give to people to take home with them to record their sleep patterns. You can, therefore, get a minimally interrupted function in a home environment, with all the accompanying good aspects of doing that.

You can make body temperature measurements now with relative ease, with minimal interference — socially acceptable techniques of measurements — 24-hour measurements in real shift work situations. And there are methods of getting very frequent blood sampling with a minimum of interference. People can work and we still can get 24-hour definitions of all kinds of blood and plasma measures. This was considered to be a valuable field research program that should be done.

However, what do we measure in the urine? What do we measure in the blood? You have to have a hypothesis and you have to think it's important. You can measure everything; any available laboratory test can be measured. What should be measured should be measured on a concept of an hypothesis, not just measured because it is there to be measured. There should be focused hypothesis-oriented measurements.

Finally, into the laboratory. What kind of laboratory research should be done in relationship to the field work to be done? It was generally felt that there are two levels of laboratory research. One we might call applied laboratory research; that is, laboratory research in which you mimic the industrial or work situation. For example, the kind of study that we did in which we inverted the subjects' sleep for three weeks and kept them sleeping at night is not really the way people act. They don't do that when they shift their work. So, that's not directly nor immediately relevant.

If one is going to do that, say: "O. K., stay awake for five nights and sleep during the night for two days; then stay awake for five nights," mimicking a three-week acute shift situation under very controlled conditions in a laboratory, then use the other level of "basic research." Basic and applied always work in a simplified concept. Nevertheless, how does it differ, for example, if you have two days when you go back to sleep at night; two days, compared to sleeping during the day for three weeks or a month straight? So now, move in and out of these applied and basic concepts. The focus of laboratory research should then be moved back and forth into the real life situation and information gathered. Say: "Gee, that's important; let's measure body temperature. Maybe that's got something to do with how stressed they are. Or heat stress at night versus heat stress during the day. What is the relationship of severe heat stress at

night while at work when body temperature is at a low level, compared to heat stress during the day when body temperature is high?

These are focused areas that come from the laboratory into industry and, in our discussion, we felt that they are important. In an interdisciplinary broad conceptual program — unlimited everything — you should be able, ideally, to move into these kinds of situations from laboratory to real-life work situations.

Finally, we felt that individual differences is an important area for exploration, both in the laboratory and in the field situation: the issue of where people are when they enter the work situation — what their phase is — whether they are so-called larks or owls, morning or evening types, and correlation of that with personality types.

We also felt that perhaps an essential predictive factor of those who would adjust or not adjust to shift work is the whole concept of self-selection of individuals in the process of a phase-shift.

## **Group II**

*Dr. Olguin:* I'm Jorge Olguin from Du Pont and I was volunteered as recorder for our group. We started by trying to establish some of the varied questions that we'd like to answer in our discussions. I'll list some of them, not necessarily in order of priority but rather in chronological order.

Some of the questions were: What is the significance of psychological and social stress and what role does the immediate environment play in the performance of people on shift work?

Another one was: How do we define the problem? Take a look at the broad picture; then, very similar to what Dr. Weitzman has discussed, the work in the field versus that in the lab. Essentially, the conclusion reached here is that survey type work and lab type work are complementary and it is necessary to have them both.

And then a very important question: What generalizations can you make? How specific can you be? Are only general conclusions going to be drawn or can some of them be applied to specific situations?

Based on all of this, it was more or less suggested that what we really needed to do was to isolate and identify factors that have an effect on shift work. How are they interrelated? Are there any hidden variables? It was pointed out that there are some hard facts; that there is some information specifically on the effect of shift work on longevity and the effect of critical age; that this information is available; and that we

should determine how we can best apply it and how we can get it to the "man on the street."

I'd like to share with you our tentative list of the effects and factors involved in shift work. It was felt that one of the things that has to be done is to list risks more or less in order of priority.

One job classification in shift work would be work where risk is at a minimum, where the only things you might have to consider are psychological and sociological consequences. Then there is the type of work where the risk is only to the worker himself. A third category is that in which there is risk not only to the worker but to others associated with him. Last, there is work where there may be variable outside interferences.

Typical types of jobs were chosen, the implication not being that they were the only types of jobs but that they were being used as examples. One is the airline pilot's job in which there not only is risk to himself but to his passengers and in which there can be severe variable outside interferences. And there is the case of miners, for example, where there may be risk not only to themselves but to somebody else, but where outside interference is more or less at a minimum. The hospital worker case — and this can be debatable — might be an example of one in which the only risk is to himself. Then you have the case of the worker whose job it is to pack cotton into boxes; obviously, there's not a great degree of physical risk but there may be other consequences.

Then we listed effects and factors. Some of the effects listed are: life span, resistance to low stresses, morbidity and health; in other words, performance and response to drugs or exposure to chemicals. Factors — not necessarily in order of priority — are: sleep loss, social disruption, circadian desynchronization which may be transient, and health risks from a job accident. And there is a category of individual whose present health could be influenced by his age, sex, prior health history, and his own personality.

Schedules of shift work and the concept of polarity were brought up; also, the fact of individual tolerance. We considered the effect of training and education on the individual worker especially with reference to motivation. Then you also have the competing environmental synchronizers. And the effect of drugs, the point that more drugs may be taken by workers on shift work.

Our discussion was not complete because we ran out of time. But this is essentially where we had to stop.

### **Group III**

*Dr. Wilse B. Webb:* Sleep disturbance is one effect of shift work and presents a potential health hazard. The physiological "cost" of working during one's usual sleep time is higher than during the usual diurnal work

routine. Safety may also be reduced; monotonous tasks requiring little physical or mental expenditure are performed most poorly when sleep is disturbed. High response tasks are least affected.

Night shift workers demonstrate a decrement in mental and physical performance for about one week following commencement of night work. Their sleep usually is continuous, but less in duration than on day shift. Socially, these persons have afternoons available to spend with their families, but the usual sleep time in the morning may interfere with family routine if sleeping quarters are not isolated from household noises.

Afternoon shift workers typically do not sleep in one continuous stretch. Sleep is usually postponed for several hours after getting off work. Nocturnal sleep tends to be a several hours' "nap," then an awake and active span in the morning. The complement of sleep is usually not totally made up by an additional few hours' "nap" in the afternoon. The resulting "split-sleep" pattern is poorest for quality of sleep.

*Dr. Jadwiga Wojtczak-Jaroszowa:* At submaximal exercise, the difference between day and night oxygen consumption is negligible. However, at maximum work levels,  $O_2$  consumption is significantly lower at night, suggesting a diminished maximal physical work capacity at night. That is, the physiological "cost" of maximal work is greatest at night. This effect is greater in males than females. Recent night-shift routines in the USSR have experimented with a scheduled break in mid-shift for physical exercise. This activity span apparently stimulates mental and physical performance throughout the remainder of the night shift.

*Dr. Erhard Haus:* Retrospective research on effects of shift work has been confounded by lack of comparative data and incomplete reporting of present and past histories of shift work and shift workers' health. Hence, research on physiological, behavioral and social effects of shift working should focus on a large-scale prospective study. A multivariate approach is desirable at the outset. Ideally, from non-invasive ambulatory monitoring of a number of variables one could describe their circadian parameters and phase relation with those of performance and safety. One or a few variables might be chosen which are related to performance and/or safety and health and continue monitoring these throughout long-term studies. Interactions between circadian system stage and certain toxic industrial chemicals might only be carried out in laboratory animal models.

*William Gruen:* Miniaturized ambulatory monitoring systems have given us the capability to non-invasively measure many physiologic variables in an industrial setting. From the potentially great amount of raw data, we must develop direct methods of data analysis and display without manual intervention.

*Dr. Frank N. Dukes-Dobos:* In response to Dr. Webb's comments concerning the negative results on laboratory studies which tried to identify

the health effects of phase-shifts, I should like to point out that in the laboratory they usually observe healthy young subjects. If they would include older people and those whose health status is marginal, just as can be found in most groups of shift workers, then they might find some health effects. Some studies reported a higher frequency of common complaints, such as dyspepsia, fatigue, headache, and irritability among shift workers. And medical monitoring of shift workers may bring about more information on health effects.

Regarding a discussion on shift work acting as a sensitizer to harmful effects of other stresses in the working environment, I believe that the high prevalence of heat illnesses on Mondays in hot plants may, in part, be due to the fact that Monday is the first day of the work shift and the workers have not yet adapted to the new rhythm; thus, their physiological adaptability to heat is less efficient.

*Dr. Lawrence E. Scheving:* A chronobiological approach to the study of problems of shift work has an advantage in that one can monitor certain physiological, psychological and biochemical variables and quantitatively demonstrate what actually is occurring to a particular variable during a span of shift work. From our own investigations on phase shifting, we have found that some rhythmic variables shift quickly while others are quite slow. Consequently, one can assume that at least some internal desynchronization does occur between variables which may or may not be interdependent. The point to be made is that in undertaking such a study, one must not select only one variable to monitor (such as body temperature which phase-shifts comparatively fast) and upon which to interpret what is happening — a multivariate approach is absolutely essential.

The data available at present are sufficient to give a good idea of the temporal organization of human beings living on a more or less conventional routine (three meals a day and six-eight hours of sleep per day). From our own studies on a host of variables from several different populations which include, among others, a group of healthy young men, a group of patients with leprosy, and a blinded population (all living under the same standardized routine) we can be reasonably sure of predicting when the highs and lows of a given function are apt to be occurring in time.

What is missing are similar data on a sufficient number of variables on persons actually subjected to shift work. Until such information does become available one can do little more than speculate on what happens to the temporal organization of the shift worker; obtaining such information is of paramount importance to understanding the mechanism of the shift work syndrome.

If and when such studies are undertaken, in addition to using a multivariate approach, there should be included in the study representa-

tive groups of different ages and sex and great care must be given to what their work shift history was and also to the types of work (physical and mental, strenuous and light work). If simultaneous studies are not feasible initially, a limited study should be carried out on those populations where the consequence of error would be the greatest. The problems of logistics, consent, etc. are the major obstacles to obtaining information of this nature. To adequately investigate the problem of shift work will require a monumental effort; anything less is apt to be an exercise in futility.

#### Group IV

*Dr. Thomas J. Murphy:* I think I can characterize the approach we took as being fairly "rock bottom practical." We agreed immediately that we had to make some small start on this large field; and I characterize this as a "field" because we really don't know, I feel, in a net effect whether we have a problem or not.

And, second, we agreed that it should be a multi-stage approach, that one stage would lead and direct us to another. I think another practical thing is that it probably should be under the supervision of a full-time NIOSH person so that it doesn't end up as a pile of statistics in a manila folder on somebody's desk.

We agreed that accident data appear to be the most available immediately and are the most convincing of data. And it happens that there are some sources for data which are fairly immediately available with what appear to be some minor changes in their data for gathering. There are three of these.

Probably the most available and most appealing survey is the one conducted by the Bureau of Labor Statistics and Department of Labor. I'm not sure of the periodicity; what is it, Dr. Owen?

*Dr. Owen:* Each male.

*Dr. Murphy:* Each male on shift work is asked a question. This data base really encompasses all of American industry. It's a structured survey — 25,000 people — and from that we can determine the effects of present absenteeism on various occupations and industries, with the addition of certain questions in the survey. We could, for instance, ask the time of day an accident occurred, the time of the shift, the type of shift system a person was working, and whether the accident was person or equipment caused. There are some practical problems with this approach, in that there are some determiners as to whether these kinds of questions can be asked by the Department of Labor. Industry and labor, for instance, might have something to say about that.

There also are the OSHA statistics on those reportable accidents that are being kept by certain companies. I understand that this is not covered

— government employees are not covered here — and this is an important omission.

The third base is trade associations and these people already are keeping statistics of this sort. We feel that there is some incentive to industry for answering such questions in that accident rates do determine insurance rates and compensation rates; any indication of methods to reduce accidents would be compensation for them.

This should help answer the question of whether there is any evidence despite all the compensating factors or greater frequency or severity of accidents in any particular occupation or industry or in the country. And it would allow us to zero in on particularly sensitive and vulnerable industries and occupations.

This type of aid might also point to what to do with the data, in that it might indicate differences in one type of shift systems which should promise a reduction in accidents and point out occupations which are particularly sensitive to shift work.

As far as assessing health effects goes, we felt that this was a longer term and more difficult problem but that part of it might be assessed by the same sources and absentee data. One panelist suggested, along with the present assessor, the public health nurse might be sent to make an assessment of health, perhaps even take some measurements. One participant felt strongly that continuing research should be made both on humans and with animals.

*Dr. Shepard:* Thank you, Dr. Murphy. As I moved around a bit to some of the meetings, I came up with some ideas and some things that I'd like to pull together briefly from what was said this morning. As I mentioned yesterday — and it has come through from at least three of the four speakers this morning — we can't overemphasize the importance of individual differences in social and psychological factors in terms of physiological rhythms. What specific hypotheses are we making in terms of depressions as possible factors? What are our hypotheses regarding these when we construct a questionnaire?

I think it was Dr. Weitzman who mentioned avoiding the important topic of how to measure well-being. Perhaps that is one of the paramount difficulties in this field, that we can look at someone who has an ulcer or is severely depressed and say it's due to his shift work. But, if someone is doing fine, is working fine and doesn't have complaints, what is going on with him? This is an aspect of what Dr. Tasto presented yesterday with the breakdown of four types of workers — not just shift workers — which is part of the contract that currently is getting underway in our section.

The career shift worker, I think, is someone who is a segment, some-

one who has worked for 5-10 years or longer on shifts, who seems happy with it but goes back to the diurnal cycle on weekends.

What are his rhythms like? I know there are a number of studies underway, attempting to get this information, but it seems to me that we need a base of information on a number of these workers. Why are they happy on shift work? There are a lot of psychological reasons which Dr. Mott presented earlier. What about their rhythms? Another speaker suggested that true inversion does not occur. This is one of the arguments that is used in favor of rapid rotation.

Getting back to the issue of individual differences, the question of circadian rhythms, the question of the lark-owl phenomenon as it can be measured socially or psychologically in terms of introversion extroversion and physiologically in terms of when temperatures peak and people's different feeding cycles requires further investigation.

I should like to close by leaving you to think about the question of how to measure well-being and the individual differences that are important in your field. When you come to the group discussions, I hope the outcome will be that you can come to the podium and tell us from other disciplines, if we are going to do a good study, what are the variables from your discipline that we must look at that should be included as basic variables in a good research design.

*Dr. Ross:* I am Don Ross, a teacher in psychiatry and environmental health. I teach occupational mental health to occupational physicians and nurses and to NIOSH trainees in industrial mental health. I'd like to provide a little input at this point in the hope that this might be considered further in the afternoon discussions.

I want to express appreciation for all I've been learning from the deliberations so far in terms of practical occupational mental health matters. And I've been getting an impression that shift work is for the birds. That doesn't mean I think that we could do away with it. It does mean that I am intrigued with the idea of different shifts for different birds. I'd like to add, in addition to the morning larks and the night owls, the starlings who are very busy in the evenings, at least here in Cincinnati. I should like to see more investigation along the lines that Dr. Akerstedt reported about methods of measuring different types of people in relation to the possibility of trying them out on different shifts.

Now, any field studies along these lines would have to be arranged with unions as well as with management, though there is some rationale for the union policy of an individual having seniority before he can get off an evening or night shift. I think there is some rationale in terms of critical age, but there would be excellent possibilities of having studies done toward selection for optimum shift assignments for different individuals.

To come back to animal experimentation, I wonder if it would be completely impossible to have some studies done on actual larks, starlings and owls. We wouldn't have to put salt on their tails. We have been able to do research with pigeons — even psychological research — and I think it would be very interesting to see what the circadian rhythm is in these different types of birds.

*Dr. Shepard:* That's a very interesting point. Now let's consider something that a number of people have addressed in their talks this morning, the issue of longitudinal vs. experimental vs. field study and some of the different advantages of each.

Regarding the idea of the longitudinal study and this again seems to be such — I'm not sure what the differences are between this country and Europe in terms of the interaction between government and industry or government and health service providers — but longitudinal studies on health factors in England (and I know of some of the Scandinavian countries) seem to be much more efficiently conducted and the funding is better coordinated, than in this country. Perhaps some of you can give us tips on how to go about organizing these things.

The experimental field studies emphasize, from my perspective, the importance of identifying the groups, in a sense, for an experimental purpose. We are looking at shift workers — career shift workers — people who perhaps have been shifting for a couple of years but who (at least some of them) are still manifesting problems and people who are new to shifts and are having problems or are going to have problems. What are the differences among these groups? We talked about a lot of social and family factors, psychological factors (and a number of different scales have been measured), physiological problems in terms of desynchronization and certain health complaints — gastro-intestinal, ailments of sleep, and adjustment problems. A research technique I believe got mentioned in terms of sleep logs, a tool to get an idea of how people sleep, how shift workers sleep. A number of shift workers in research indicated that some people nap, taking a sequence of naps during the day rather than one extended sleep time.

In the safety area, the emphasis seems to be on the need for experimentation and determining the factors which actually might predict, or seem to predict, the likelihood of accidents in terms of attention factors.

In our disciplinary meetings, we'll want to consider: What are the aspects of each field that are critical, that are most important when we leave this symposium; what is it that you want people from the other disciplines to know about your field, to take home with them, to have in the backs of their heads as they design future experiments in terms of shift work research?

Our current study that is going to be getting underway will be

covering a number of industries. I've noted the overwhelming complexity of the field that's been presented in the past two days. I don't know if anyone could identify a good one, but we should be looking for some industry in which the actual task is as similar as possible around the clock rather than one in which the night people do different things than the day people. If we could reduce the variance introduced by differences in the past, then the variables that we are concerned with might be more easily isolated. We'd lose some generalizing applicability to other industries and to other kinds of shift systems, but we need to start somewhere.

**Session III**  
**Disciplinary Meetings**



**Topic: Perspectives on Shift Work and Future Research Plans —  
Physiological, Medico-Toxicological, Social-Behavioral and Safety.**

*This symposium has presented a number of perspectives on the health and safety problems of shift work. The morning session emphasized the interdisciplinary sharing of ideas, directions and problems. Now, we shall consider the unique contributions of each field.*

**Guidance**

Thinking back over the input from the other areas of specialization, what changes have occurred in your understanding and evaluation of the role of your field in research on the health and safety consequences of shift work? Re-emphasize the unique contributions of your field. Discuss the aspects of the other areas that must be considered in your research, and the aspects of your area that would seem to be essential to their research projects.

Concentrate on answering the following questions this afternoon:

- 1) What is the primary contribution your field can make toward identifying the health and safety consequences of shift work?
- 2) Considering methodological, instrumental and theoretical difficulties that exist in your field, what problems will be encountered in conducting and evaluating future research? How can these problems best be handled?
- 3) Will practical contributions to understanding and reducing the health and safety consequences of shift work emerge in your field in the next one to three years? What directions will this research take?
- 4) What knowledge should the other disciplines take away from the symposium concerning your field and its research tools? Summarize this for the final presentation and general discussion.

Each small group chairman or his designates will present a brief summary of his group's session to all the participants. There will be some time for questions or comments following each presentation.

**Social-Behavioral Group**

*Dr. Owen:* In our social behavioral group meeting, the degree of consensus reached was typical in a group of social scientists but I'll try to lay out the major points of issue as clearly as possible.

One question that was raised was: Should the concern of NIOSH be confined not to the effects of shift work on work or health but rather to

broad effects of shift work, for example, to divorce rates, traffic violations, etc.? We agreed that, while the latter are interesting, the effects on the worker are the paramount concern. However, the continuing strong interest was placed on the effects of shift work on the rest of society and the role that shift work research could play in bringing that out, more specifically effects on accidents and effects on industrial efficiency.

If that point of view is adopted, we should realize that most jobs rarely tax the individual's full capacity. Occasionally, some jobs never tax it at all. In some shift work jobs, neither the day or night shift jobs are that taxing. In many others, the demands on the day shift may be taxing but those on the night shift are fewer than those on the day shift. In consequence, the most obvious utilization of laboratory research is looking at the physical limits with taxing jobs, night jobs, where loss of efficiency will lead to serious consequences to society. The airplane pilot whose physical responses are inadequate when manning his plane on a long night flight is the obvious example.

However, another point of view which also was, I think, accepted by everybody is that it also is important to consider the welfare of the worker for his own sake. Some mention was made of the fact that it is possible, at least in theory, to redesign most jobs that require 100% of a worker's capacity on night work so that a smaller percentage is required.

Despite our feeling that the primary emphasis of the research should be on the effects of shift work on the worker, there was a consensus that we ought to say something about the effects on the family and on larger society, as well.

We had other specific results of our meeting; for example, suggestions for Dr. Tasto's research which we hope will result in his incorporating some questions on whether the respondent was a morning person or an evening person and whether he had difficulty sleeping and other topics of interest.

*Dr. Shepard:* Thank you, Dr. Owen. I wonder if there are any comments, or if anyone from the Social-Behavior group would like to add anything.

*Dr. Tasto:* I'd like to add that an interesting design perspective — that would be applicable not only to social scientists but also to people studying any dependent variable as a function of shift work — is a critical incidence approach. In this approach, we would study people who were clearly not adapting to shift work and, at the same time, take a look at some who were adapting and observe the differences on any number of variables to see whether they round out the paradox. This would require that we include non and adapting shift workers, non-adapters who

are shift workers and who are not shift workers and adapters who are shift workers.

That tells us nothing about the magnitude or frequency of the problems, but once we get a handle on the important variables of the differences that do exist, at that point it becomes possible, from an epidemiological perspective, to study frequency magnitude.

### **Safety Group**

*Dr. Smith:* The first question that Dr. Shepard developed for us was a real humdinger: What is the primary contribution that safety can make toward identifying health and safety consequences of shift work? We had a varying amount of opinions about what our contributions could be and I'll enumerate them.

The first contribution is one that is very important — you heard about yesterday — and that is examining the human abilities and performance relationships to shift work and safety factors. There is ongoing research on this — Dr. Colquhoun reported on that — and we feel it is very important.

In discussing bringing currently developed portable laboratories instrumentation into the field, it was pointed out that NIOSH and our Behavioral Motivational Factors Branch have a number of studies that have used portable human performance equipment. I noticed in the literature that there is a lack of use of this type of equipment in field studies on shift work. It would be quite easy to take the equipment that has been developed for us under contract and apply it in this area.

The third major area we felt was important is the utilization of presently recorded injury data for three purposes.

First would be the determination of the relationship of shift work to safety performance. This would be simplified by the new OSHA reporting regulations and the fact that there are a number of large companies that go beyond the OSHA regulations and keep track of the time of day a worker is injured, information on the type of shift he is on, etc. We feel that there are data available pertinent to examining the accident experience on different shifts and that it would be important to get this information.

The second thing dealing with recording injury data would be to determine the occupational groups that have the greatest risks or hazard of risks. And, of course, we can use the same data to examine the differences between our air pilots — we had one in our group who felt that there was a significant need — and other individuals who have a high

risk factor. With this information, we could set priorities for which group should be examined first and determine varying solutions for each group, because we all know that different jobs bring about different demands which make for different solutions to be needed.

Third would be to determine the hazard characteristics on the jobs — specific jobs — that are most related to shifts and to accident occurrences. That is, the same job on different shifts may have different hazard potentials involved in performing the same tasks. Then, what are these and what is the incidence of this?

The fourth thing we felt was important in terms of answering the question put forth in terms of contributions is in the area of safety — and this relates definitely to our occupational safety and health act. Putting forth standards related to scheduling and scheduling problems associated with performance, man's abilities, life habits, etc. related to shift work is a very important issue that we felt could be handled at this time, based on some of the information put forth at this conference.

In terms of the second question, in considering methodological, instrumental and theoretical difficulties, what are the problems encountered in conducting research? How could these problems best be handled?

We felt, first of all, that bringing more sophisticated tests from the laboratory into the field was needed. As I indicated earlier, we have developed within NIOSH a performance test that is more sophisticated than has been used; however, this still is not as sophisticated as what is being used in the laboratory. We feel there is a real need to develop instrumentation to be brought out into the field to be able to take the type of sophisticated measurements that are needed to be able to examine the multitude of interaction effects that occur on the shift work problem.

Second, we feel there is a lack of methodology along with the lack of instrumentation for examining the interactive effects of multiple stresses such as environmental stresses, social stresses, job stresses, and management stresses that affect the shift work problem.

Third, we recognized the need for developing non-invasive type methodologies for examining the variables in which we are interested — the physiological and psychological variables.

Fourth (and this is the one we in NIOSH feel very strongly about and sometimes feel a pinch on) is getting cooperation in conducting studies and taking measurements — cooperation not only from employers but from employees, from unions, from management groups, trade associations and researchers. There just seems to be a general difficulty here

(at least, we in our group felt there was) of getting into critical areas where research needs to be done because we don't have access to the individuals to whom we need to have access.

In terms of the third question: Will practical contributions to understanding and reducing the safety consequences of shift work emerge in our field in the next one to three years? And what directions will they take? The answer is yes, and the directions will be quite varied.

First, there will be information on the comparison of shift work system consequences; that is, differing shift work systems on safety and health — particularly on safety.

Second, there will be research identifying changes that occur in the mental processes due to different shift work systems and due to shift work.

Third, there will be better statistical information coming from employers with which to define the shift work problem and shift work effects on accident rates.

Fourth, there will be research relating circadian rhythm shifts to worker performance. There already are results on this study which indicate that there is a relationship between worker performance and changes in the rhythms.

Fifth will be the development of methods for measuring work load and shift work interaction effects on performance.

I think that is quite a grab bag of different types of data and information to be coming out and one of our problems is integrating this information. However, I was very gratified to see that there are a number of researchers who are actively involved in this field and who will have some real hard results within the next one to three years.

The fourth question, of course, was the toughest: What knowledge should we — designated the safety group — pass on to the rest of you, the physiologists, the MDs, the hygienists, the sociologists, the psychologists, as to what we think you should look at, what we think you should know about safety in terms of shift work? We have a number of things:

The first point is that we feel there is a real need for objectivity in the measurements of data, particularly in the area of examining worker-subjective reactions to particular systems.

Second, we feel there is a need to have multiple types of variables measured and correlated at the same time, rather than looking at single variables.

Third, there is a real need to include safety and accident characteristics and matters into the research that the physiologist and sociologist and psychologist is examining because they would be very easy to include in your studies.

Fourth, we feel that more applied research should be conducted. We've heard a number of researchers talk about research in very laboratory-type settings, kind of getting away from real life, and, while the researcher sees them, it is more difficult for an applied safety person to see them. And we would like to see some real-life validation of some of the techniques that were discussed.

The fifth is the most appropriate at the end and that is more cooperation among the different disciplines. We need more get togethers like this where we can sit down and talk about mutual problems and kind of throw a rock back and forth at each other but, in doing so, get a better feel for the contributions each of us can make.

#### **Physiological Group**

*Dr. Bethea:* The health and safety consequences of shift work can be identified through studies on man and animals under laboratory and field conditions. Suitable research can determine the alteration of normal physiological rhythms, including sleep-wakefulness, caused by shift work and the resultant influences — positive and negative — on worker health and safety. In man, short-term effects of phase-shifting are the desynchronization of circadian rhythms, alterations of the sleep cycle, and performance decrement. Chronobiologic studies, primarily on animals, have shown that circadian rhythms can make life and death differences with regard to life span (both to lengthen and shorten), to the resistance of the organism to acute or chronic exposure to toxic elements, and to pathogenesis. Longitudinal studies on both animals and man will provide a better understanding of the long-term effects of phase shifting. Knowledge of the relationships of physiological circadian rhythms to the health and safety of shift workers will lead to manipulation of the circadian state as through mean timing to maximize the beneficial aspects of phase-shifting and eliminate or minimize any detrimental effects.

Methodological, instrumental, and theoretical difficulties encountered in physiological research are steadily being overcome. The statistical surveys of necessarily biased samples and sporadic "fishing trip" data are being complemented by experimental animal models providing hard and pertinent facts as in the papers presented at this symposium. Interpretation of chronobiological data by (subjective) examination of time plots is being replaced by analytical statistical evaluation.

The development of standard measurement methods will allow cross-study comparisons among research groups. While the support of studies concerned with the collection of 24-hour data is more justified than that

of those which ignore rhythms altogether, collected data must not be stored in a form unusable for further analysis and thus lost for evaluation by those interested in chronobiology. Data collection is being aided by the development of ambulatory monitoring techniques which greatly increase the potential for field studies. Use of solid state "memory" storage in the near future will eliminate some of the problems of data conversion and reduction. Further progress in analytical procedures is needed to facilitate the handling of the large volume of data obtained from continuous monitoring equipment.

Developments in methodology, instrumentation and analytical procedures will further the theoretical understanding of the causal relationships between rhythms and of how these affect the safety and health of shift workers. Chronobiologic studies have produced many, as yet unanswered, theoretical questions; i.e., how can individual differences, such as those found in "lark-owl" types, be explained? Why does alteration of hormone rhythms raise the overall resistance of an organism in toxin studies? Does desynchronization of physiological rhythms with phase-shifting cause sleep loss and alteration of sleep quality? Or does the alteration of the sleep cycle cause the desynchronization of the physiological rhythms? How do both factors affect performance? What are the psychological effects on physiological circadian rhythms? The answering of these and other questions will provide many clues to the effect of circadian rhythms on the safety and health of shift workers.

Research in the next few years will begin to answer the theoretical questions so that practical contributions to understanding and reducing any health and safety consequences can be made. Inclusion of the owl-lark difference as a factor in future research will make it possible to determine the significance of this difference and how it might be used in shift worker selection. Preliminary studies, for example, indicate that the peak in body temperature may vary between these types. Perhaps there also are differential responses (in these individuals) to phase-shifting or to conditions that might lead to free-running of their rhythms.

Other research areas will include the effects of exercise and digestive disturbances on shift workers. Recent evidence has shown that the amount of prior exercise can affect performance. Studies are needed to determine the size of any differences which exist between shifts and exactly how performance, health, and safety are affected. In view of conflicting results on the digestive disturbances associated with shift work, more research is needed in this area particularly with regard to how meal timing could be utilized to minimize detrimental effects.

In addition, longitudinal field studies of shift workers are needed to further determine the actual positive and negative health and safety factors involved. These could be coordinated with socio-psychological

research to correlate or perhaps even establish causative relationships of the physiological measurements with psychological performance and mood with appropriate application to different industries, age groups, and shift schedules.

Because an interdisciplinary approach is important for the full understanding of the health and safety consequences of shift work, certain basic physiological points should be considered in all research.

Perhaps the most important of these is that an organism's physiological state cannot be determined by a single measurement; therefore, some consideration of circadian state should be made. Autorhythmometry can be used as a simple means of monitoring some basic physiological rhythms such as heart rate, body temperature, the blood pressure. Records of changes in the sleep-activity cycle should also be maintained and, if possible, some measurements should be made of sleep loss and quality. These data will enable correlations to be made to other research.

In addition, when phase-shifting is involved, it must be remembered that circadian rhythm resynchronization depends on several factors: the number of shifts and their intensity and direction. Documentation of chronobiological state; i.e., times of treatments, light-dark cycle, etc., should always be given even if rhythmic variation is not included as an experimental factor so that data obtained can be related to other past and future research efforts.

#### **Medical-Toxicological Group**

*Dr. Moore Ede:* In summarizing the discussions of our group, I could take a safe route or a dangerous route. The safe route would be to give you a talk of generalities, such as we need more good interdisciplinary research, done well, which would give clear answers to the key practical problems and would bring the benefits of this research as soon as possible to shift workers and to industries. The dangerous route I could take is to come up with a specific proposal which, of course, leaves one open to criticism but I think it's probably a more healthy approach to take at this time.

Believing in living life dangerously, I'll turn to discuss a specific study of the sort which our group felt was necessary for NIOSH to undertake. We really wanted to get some good clear data on these questions so that changes could be made both in shift work schedules and in the selection of individuals and so the determination of the groups most at risk could best be done.

The study would be similar to the Framingham Study. For those who may not be aware of the Framingham Study, this was a study on coronary heart disease which examined the incidence of this disease in a

community in Framingham, Mass., following the population over a period of years — 10 years or more. With both studies — this large number and also more intensive studies in small groups of this population — they were able to identify the major factors that determine risk of developing heart disease and mortality from heart attacks. Much of the data we have today on heart disease and risks and the main factors that increase risk and heart disease were determined from studies such as the Framingham Study.

The study we would propose would attempt to get around some of the problems of the very limited studies done to date; none of any reasonable size have been done in this country. This would be a study which would aim to identify the major medical effects of shift work, which individuals were most affected and most predisposed, what the predisposing factors were, which individuals were best suited, what sort of training could be done and what sort of shift work schedules would produce the least mortality and morbidity.

In discussing this study, obviously I'm only going to be able to sketch over some of the outlines of it, but clearly one would want to be working with a large number of individuals who were subjected to shift work and other individuals doing similar jobs with similar degrees of risk and similar requirements of manual or mental energy input as control subjects at the same time. One would want to have a large study which included individuals of varying ages, sexes, races, that would not exclude individuals of prior health states because I think it's very important to study, for instance, whether people with latent diabetes or latent hypertension have their medical problems accentuated in response to shift work. Since many shift workers have these problems, it is essential to include these individuals in the study as well. One would also want to look at individuals with different personality types and in different geographical areas and in different general environments in the U. S. The feature of the study, therefore, would be to look and try as much as possible to get an idea of what are the major factors that influence the effects of shift work.

But, to consider a bit more about this study; basically, what might one be able to do? There would be some things which would come out relatively soon and there are some things which would take five or 10 years to come out in this sort of study.

The things that could be achieved in a year or so are changes in accident rates in industries where there are significant numbers of accidents and where monitoring techniques already are established. As we have a bit of an inkling from some of the preliminary data we've seen from Kodak, you could get indices of some changes in performance, indices in social effects, and these certainly could be picked up in one

or two years. Some psychological changes, could be noted, too, perhaps, and also some behavioral changes and changes in the instance of taking drugs and other medications.

If one were interested in the question of mortality, of life expectancy; if one were interested in questions of morbidity, the incidence of disease and the exacerbation of prior disease, one clearly would have to follow this population over a longer period of time.

We can see many problems here; for example, there are some questions that must be answered and may be answered in this contract which recently has been started from NIOSH, which is examining the shift work schedules in this country and getting some idea of the different types of schedules that are used.

Now, using these particular schedules, one would want to look at the type of work, particularly in terms of the consequences of error, whether the individual himself is at risk from error, whether others are at risk, whether no one is at risk, whether it doesn't matter whether he falls asleep at his job or whether it does matter. Obviously, one would want to look at different types of shift schedules both in terms of the polarity, in other words, do they move from C to B to A or how frequently do they move, and also in terms of other environmental conditions at the same time. One would want to look in a number of different industries, selecting industries that were representative. And probably one would have to select industries where there already was some sort of union and management interest, as there has been recently in air traffic control, in having this sort of study performed.

In terms of basic design of this study, there obviously are a multitude of questions involved here that one would want to answer and could answer in the framework of this study.

First, the morbidity, mortality effects could be determined by complete medical examinations, biochemical screenings, psychological screenings, on a yearly basis of this whole population. That would be comparable to the sort of thing that was done in the Framingham Study. And, over a longer period of time, follow a large group of people and control age match, sex match, and so forth — controls in which one should be able to detect whether there are differences in those groups.

The studies at the same time of performance characteristics of physiological changes would have to be done, most likely, in smaller intensive studies; in other words, sub-populations of this total study. These would be populations of individuals — special volunteers — and maybe only a dozen or less who could be studied intensively, both longitudinally and over a short period of time with multivariable studies. Using this sort of approach, one could attack the other very important portions of this whole problem. One could attack the problem of what are the mechanisms

involved, because, if there are shift work effects that are significant, they should come out in this study.

But what are the mechanisms of those effects? We've heard some initial hypotheses. We don't have many; we have a few. Some initial hypotheses as to mechanism would be an important part of this whole study and would be studied intensively in small groups.

I'll just give one as an illustration. That is that individuals who are in a state of internal desynchronization for a significant period of time of their life span or of the percentage of time variables are oscillating in different frequencies. But those individuals are more at risk than others and, clearly, one would like to look at whether, therefore, one would want to correlate that with different shift schedules.

If, for example, in one shift schedule, the individuals were virtually always permanently desynchronized in between various marked physiological variables and if that particular group also were the ones that showed the greatest morbidity and greatest changes in performance, then, clearly, that would be an important point to establish.

I think that, if you really want to know the answers to these questions, you want to come up with some hard specific manipulations of shift work schedules. If you really want to come up with selection procedures for choosing individuals who are best suited for certain schedules; if you really want to start applying this information, I think we have got to have these sort of data first and they probably have to be organized in a fairly comprehensive study of this type which looks at the overall general effects on the large population and you need the large population to detect some of these smaller changes, and detect the level of the variances of the population from other effects. We're concurrently using this type of population for study of physiological changes which might be future indices of morbid effects.

## CLOSING REMARKS

*Dr. Shepard:* Pulling some things together from this rather comprehensive study that came out of the last group, I think the purpose of this symposium was to bring together representatives of a number of disciplines who, in a sense, had not come together as much as they might on this issue, to stimulate interaction, understanding, and, hopefully, to generate research across disciplines.

The emphasis that I think has come out in the past two days is the issue of individual differences, the importance of identifying shift workers who do not adapt, those who, in fact, suffer health consequences. The problem is with isolating these and perhaps getting those who have health consequences and looking just at them and saying that these have indeed been affected and their rhythms have desynchronized. Then, perhaps we can make a connection. The desynchronization obviously must be the cause of the health consequences in an experimental design.

I think we must include those workers who adapt well to shift work. We may find, in fact, that the same desynchronization exists in their basic physiological rhythms and that, therefore, there is some other factor operating, perhaps social, perhaps at a deeper level physiologically, neurochemically.

The emphasis on health consequences in terms of medical problems, and in terms of some of the psychological problems which Dr. Mott alluded to, perhaps in terms of depression are things that need to be stressed.

The comprehensiveness of this study and the budget have led me to think back in terms of some of the issues which were raised by Dr. Tepas yesterday regarding experimental design. I'm oriented in this area myself toward field studies, I think, because we need to work with real shift workers. We can bring them into the laboratory, but we must study the real shift worker because of all the vagaries of his existence.

If we can, we should identify an area of shift work where the task is as similar as possible around the clock, where what the worker does in the evening and at night is the same as what the worker does during the day, again for comparability in the results — comparability of the tasks, in terms of the effect on his health. This is something of paramount concern.

A number of people in the physiological, medical and social areas also have addressed the question of possible health consequences; what do we do in terms of eating patterns, sleeping patterns, family patterns? Perhaps guidelines should be formulated to help the family facilitate adjustment to the shift schedule. This seems to be perhaps the second step in something we can look forward to as an outcome of future research.

Finally, the last comment would again relate to something that Dr. Mott and Dr. Owen also brought up about the importance of the cooperation of unions and workers, as well as management, in resolving the issues of the health consequences of shift work. I know Dr. Halberg had a letter from one company which invited him — or suggested perhaps that he could come in — to change the shift schedule that currently was in operation. This kind of *in vivo* situation, in which you can alter the shift system and measure the before-status and the after-status of the workers, could, if it's in the best interests of the industry, be something that could be a great opportunity for the social scientists, the medical researchers, and the physiological biologists.

*Dr. Rentos:* I personally want to thank all of you — speakers, discussants, our invited guests — for participating in what appears to have been a very worthwhile symposium. I think we've made some inroads. We brought scientists together who relate. And, hopefully, we'll get down to practical aspects now and perhaps solve some of these problems.



# Appendix



# **A THEORY OF BIOLOGICAL CELL RESONANCE AND ITS RELATIONSHIP TO HEALTH AND OCCUPATIONAL SHIFT WORK**

*Donald E. Wasserman*

In this Symposium of Shift Work and Health, several papers have been presented elucidating the areas of circadian rhythms, health in phase-shifting, toxicological correlates of shift work, accidents and injuries relating to shift work, and social-psychological adjustment problems and perspective related to shift work.

This conference has attempted to address itself to the multiplicity of micro- and macro-factors thought to affect the worker subjected to a shift work environment. In particular, I cite the presentations of Drs. Akerstedt<sup>1</sup> and Mott<sup>22</sup> elaborating respectively on the multidisciplinary and intervening variables affecting shift work; and thus, tending to focus on the potential enormity of the shift work problem and the fact that a true assessment of the impact of shift work on humans requires research on many levels including the cellular level.

Of special interest to this author was the presentation of Dr. Moore Ede<sup>21</sup> describing his work concerning the multiplicity of biological oscillators thought to be located within the body. The proposed theory of biological cell resonance is in harmony with Dr. Moore Ede's findings. Details of this theory follow later.

## *Burr's Electrodynamical Theory of Life*

In the 1930s, H. S. Burr, a biologist at Yale University, developed a new concept of biological system organization which he called the "electrodynamical theory of life"<sup>11</sup> wherein he states that "an increasing body of evidence indicates that bioelectric phenomena underlie growth as well as many other biological processes. Numerous electrometric studies compel us to believe in the presence of polar and potential differences in living systems. If this is true, it follows by definition that electrodynamic fields\* are also present. Their existence in the physical world is generally

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\*A field is a continuum of experimentally verifiable electrical vector forces defined in terms of two descriptive parameters, intensity and polarized direction.

accepted. Moreover, the formed relations of particulate matter is to a considerable degree a function of such fields.”

Burr further elucidated his biological field theory by stating that “it is reasonable to extend this (field theory) hypothesis into the realm of biology. Potential gradients and polar differences exist in living systems. If this is so, then electrodynamic fields are also present. The following theory may therefore be formulated: the pattern or organization of any biological system is established by a complex electrodynamic field which is, in part, determined by its atomic physicochemical components and which, in part, determines the behavior and orientation of those components. This field is electrical in the physical sense and by its properties it relates the entities of the biological system in a characteristic pattern and is, itself, in part a result of the existence of those entities. It determines and is determined by the components. More than establishing pattern, it must maintain pattern in the midst of a physiochemical flux. Therefore, it must regulate and control living things, it must be the mechanism, the outcome of whose activity is “wholeness,” organization, and continuity.”<sup>11</sup>

In succeeding studies, Burr and his colleagues were able to develop instrumentation for measuring these bioelectric fields<sup>6, 8, 9</sup> and then subsequently to relate these field measurements to: human female menstruation and ovulation,<sup>10, 18</sup> the tensile strength and growth of healing tissue in humans and guinea pigs,<sup>7, 13</sup> cancer in mice,<sup>3, 27</sup> and to diurnal cycles in trees.<sup>4, 5</sup> More recently, Ravitz was able to correlate bioelectric field measurements with hypnotic and other conscious states, anoxia, and insulin coma in humans.<sup>24, 25</sup>

#### *Background Information*

In the mid-1950s, this author was involved in the development of cardiac pacemakers, coincidentally also at Yale University Medical School.\* At that time (less so now), a seemingly insurmountable technical problem was the development and *in vivo* preservation of adequate sources of electrical power to keep these electronic pacemaker units functioning over long time periods,<sup>23</sup> rather than subjecting patients to multiple periodic operations for pacemaker removal and battery replacement. This author theorized at that time if the cells of the myocardium could be “tuned”\*\* to the pulsations of an electronic pacemaker, then the energy required to effectively stimulate the heart tissue would be minute compared to the energy requirements of an untuned system. In particular, if one could stimulate the cellular area known as the Bundle of His at

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\*The work of Burr being unknown to this author at that time.

\*\*A tuned system has both transmitter and receiver adjusted to the same resonant frequency (i.e., as with radio and T.V.).

its “resonant frequency,”\* this would lead to successful cardiac stimulation at very low electrical power levels, thus minimizing the need for frequent battery replacement. A series of unrelated events unfortunately prevented testing and verification of this concept of stimulating cells at their resonant frequency.

#### *Biological Cell Resonance Theory*

As an extension of this basic theory, namely that cells have resonant frequencies associated with them and that they can be stimulated most effectively at these frequencies, it occurred to this author sometime ago to ask a basic question: “If living cells have the ability to reproduce themselves (i.e., mitotic activity), then how and by what means is each cell commanded as to when to initiate mitotic activity?”

In other words, I submit that cells of a given particular organ (i.e., liver, lungs, spleen, etc.) have distinct resonance characteristics such that they are “tuned” to a particular biological clock associated with the homeostasis of that given organ; each body organ having its own biological clock with its own corresponding set of resonant cells commanded to perform mitotic and perhaps other cellular activities. Thus, cells of a given organ are frequency and phase “locked” to their respective organ clocks. Further, it is theorized that the basic reason for this form of communication between each biological organ clock and corresponding cells is to avoid organ “crosstalk” (i.e., interference between cellular receivers) and, thus, guarantee that the correct homeostatic message reaches the correct intended cells. Further, the cited work of Burr and Ravitz<sup>11, 25</sup> concerning detectable electromagnetic fields surrounding biological systems could well be the measure of this information transit between biological organ clocks and their respective cells.

It is noteworthy that in the writings of Burr and later of Ravitz, only total biological field measurements are reported. The biological cell resonance theory stated herein is a logical extension of Burr’s electrodynamic theory, since the multiplicity of resonant communication channels between biological organ clocks and their respective cells invariably generate small multiple biological fields whose aggregate has been measured by Burr and later Ravitz.

In recent work<sup>14, 28</sup> in the area of human exposure to vibration under military and various occupational situations, a corollary of this concept of biological resonance was demonstrated. The human body (as a whole) has been shown to be in resonance with external vibration sources at 5 Hz

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\*The resonant frequency of a system is that frequency where maximum energy transfer takes place between a transmitting source of oscillations (or vibration) and the receiver of such energy. In other words, both transmitter and receiver work in “concert” with one another, at maximum efficiency at this frequency.

and various other body parts and organs (i.e., limbs, head, eyes, ears, etc.) can be "tuned in" at other frequencies proportionate to the respective mass size of these body parts! Thus, it appears conceivable that the cells which form these tissues and various body organs can also have their own resonance characteristics.

The cited work of Dr. Moore Ede<sup>21</sup> concerning the concept of multiple biological oscillators appears to shed light on the possibility of a biological system employing multiple "organ biological clocks" and thus appears in basic harmony with the cell resonance theory stated herein.

Since individual biological cell mass and the size are small, one would assume that cell resonance effects and possible alterations in mitotic and other cellular activities would occur at very high frequencies (i.e., in the multimegahertz frequency range). This is true because of the inverse relationship between the mass of a resonating system and its resonance frequency. Recent experimental work by Heller, Mickey, and Freeborn<sup>16, 17</sup> has shown that, using nonthermal R.F. in the range of 5 to 40 mHz with animal and plant cells, they have been able to (1) inhibit cell division temporarily in cells grown *in vitro*, (2) induce genetic changes (mutations and chromosome abnormalities in living cells, both plant and animal, including human); (3) induce crossing over in male germ cells of *Drosophila*; and (4) stimulate breaking dormancy in gladiolus bulbs. These changes not attributable to R.F. heating due to the pulsed method of irradiation.

Additional experimental work by Baranski<sup>2</sup> on the blood forming system of small animals using nonthermal microwave radiation of 3 GHz showed increases in absolute lymphocyte counts in peripheral blood, abnormalities in nuclear structure and mitosis in the erythroblastic cell series in the bone marrow and in lymphoid cells in lymph nodes and spleen of these animals. The investigator discounts these changes as being thermally induced, rather he states "extrathermal complex interactions seem to be more probable."

#### *Relationship to Health and Shift Work*

If the theory stated herein is correct, it is not difficult to extend the consequences of a breakdown in communication between organ clocks and their respective cells to diseases, the prime example being cancer.

In particular, if there were a loss in communication or synchrony between the biological clock of a given organ and its receptive tuned cells, then, the mitotic activity of these cells could well lose their ability to multiply in an ordered fashion and thus chaotic and disorganized mitotic activity in an uncontrolled manner would result. Furthermore, Burr, et al,<sup>3, 4, 5, 12, 14, 24, 25, 26</sup> have observed changing electrical field patterns in genetically controlled strains of mice who subsequently developed spontaneous adenocarcinoma of the mammary gland.

In the case of a shift worker who works, for example, on an eight-to-five day shift and then suddenly is transferred to a twelve-to-eight night shift, his biological clocks may not be able to reprogram themselves rapidly enough to be in concert with his new work routine. Thus, the biological clocks and their respondent cellular activity probably would react to the old eight-to-five day workshift cycle; but at what cost? Barring total life inversion, some adjustment and tolerance appears to develop to this changing shift work<sup>26</sup> and in a study by Taylor,<sup>27</sup> he states that "most of the problems that do arise become apparent in the early days after starting shift work. This presumably is due to social or physiological reasons. The worker is unable to adapt to the changed rhythm of life that shift work imposes."

Potentially more problematic for the worker as a potential safety and/or health consequence of shift working, is the transition time his mind and body takes to "try to catch up" to his new work routines as he rotates shifts or as he rotates between work and rest days. His body may never really "catch up" to his work cycles. As Taylor states it: "There is good evidence to show that it can take up to several weeks for full biochemical adaptation to work at night, even though body temperature and sleep may only take a few days."<sup>27</sup> It is, thus, conceivable that a loss of synchrony between biological organ clocks and their receptive cells with man's work cycles potentially could be harmful. Only after further studies at both the micro and macro levels using interdisciplinary techniques will these points become lucid.

#### *Summary*

A theory of biological cell resonance is presented which represents a probable extension and elucidation of Burr's electrodynamic theory of life. Its potential relevance to health and occupational shift work is also presented.

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## **AN OCCUPATIONAL MENTAL HEALTH POSITION\***

*W. Donald Ross*

As an occupational mental health clinician, I have been very impressed by the reports at this symposium on animal and human experimentation on circadian rhythms and other conditions pertinent to the effects of shift work on health. These contributions to "pure" psychology and physiological pathology have some direct applications in preventive occupational medicine and even more potential contributions to further controlled experiments in actual industrial settings.

For example, the metaphor of "larks" and "owls" for individuals who are alert and active at different times of day and night, and the hint that different types of individuals can be selected by their answers to questionnaires, offer an intriguing possibility that shift workers might be healthier, happier and more productive if they were selected to work at times when they are more interested in activity and when their "stress hormones" are at a higher level. Research into "different shifts for different birds" might uncover three types: "morning larks," "evening starlings" and "night owls." Even if there should prove to be fewer individuals in the third group, this might still be practical in industries with a skeleton staff maintaining the plant from midnight to early morning.

Further animal research also is suggested. Since psychological experiments have been done on other birds such as pigeons, it should be possible to design a laboratory with free flying and perching actual larks, starlings and owls, and to measure their circadian rhythms in relation to 24-hour variations in light and dark and of noise levels. Dr. Gus Eckstein's accounts of the canaries in his physiological laboratory might suggest that these birds adapted to some extent to the scientist's "night owl" working patterns.

For our Group III of the Interdisciplinary Meetings there were some omissions from the transcribed report. For example, in a discussion of "the stress" of night shift work it was pointed out that we are dealing with various specific "stresses." My contribution on this semantic matter

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stemmed from research I had done on methods of testing for fatigue, in which it became apparent that measurements must sample the decrement in performance in an activity closely resembling the specific fatiguing activity for which one is testing.<sup>1, 2</sup>

The verbal and blackboard report of our Medical-Toxicology Disciplinary Meeting did not include my contributions from industrial psychiatry experience<sup>3</sup> and from an NIMH sponsored Industrial Mental Health Research Project.\*<sup>4, 5</sup>

Dr. Shepard, in response to the report from our group, suggested that such controlled experiments in various industrial settings would be prohibitively expensive. We did not find this to be the case in our controlled studies of employees in two organizational settings. After getting cooperation from unions and management, we were able to enroll sizeable numbers of employees to volunteer for "experimental" and control groups in the assessment of many correlates of various kinds of job-disrupting behavior. We had to include a third "modified control" group of individuals who refused to volunteer. But we were able to collect some data even on these individuals, from medical and personnel records and a questionnaire administered to their supervisors. We even were able to make economic estimates of their costs to the company, the insurer and themselves, without their participation in psychological testing or mental health interviewing.

It seems to me that similar experiments, with changes in shift assignments, could be conducted without exorbitant costs, in industries where one can obtain the cooperation of labor and management and the medical and personnel departments, if one were not too ambitious to use invasive methods of testing the volunteers, motivated to participate in the ultimate improvement of the health and social conditions of their employment.

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## CHRONOBIOLOGIC VIEW OF SHIFT WORK AND ULCERS\*

*Franca Carandente and Franz Halberg*

Thus far, hard facts concerning effects of (simulated) shift work on health stem from experiments on mammals<sup>24, 25, 38</sup> and insects.<sup>4, 46</sup> Mammalian life-spans can be altered by schedule shifts. What is of particular interest, insect life-spans can be lengthened by the "right" frequency of schedule change, just as they can be shortened by the "wrong" one.

Added work on mice now should determine more precisely the critical age for effects of schedule shifts upon life-span. Information on the factors underlying the age-dependence of such effects in other mammals may lead to meaningful extensions of such findings to human beings.

In animal experiments, one also may focus upon the role played by the body's rhythms in bearing more advantageously burdens imposed by any general or specific conditions associated with shift work. Thus, one may search for any susceptibility-resistance cycles to agents prevailing in the industrial environment and representing specific safety or health hazards. Biologic criteria considering rhythmometric tests may well serve to specify national and eventually international standards for control, e.g., of carbon monoxide, among other aspects.

Lastly, certain diseases associated rightly or wrongly with the exposure to excessive burdens — physical or emotional — have been claimed to be more frequent among shift workers, notably when work involves conditions with different interacting loads. As an example, one could focus upon apparent contradictions in the literature concerning shift work and ulcers. Doll and Jones<sup>17</sup> report on a total of 4871 workers in London, contacted first by a questionnaire and then interviewed, in which survey individuals were classified as having major, minor or no dyspepsia. The former two groups were invited to provide a detailed clinical history and to submit to a physical examination. When there was a suspicion of a peptic ulcer, this impression was checked by radiography.

In this thoroughly diagnosed study, the incidence of ulcers in men

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doing both day and night work — a sample of 364 individuals — was compared with that encountered in (3404) individuals on a regular day-work schedule. Whether one tabulates the total number of ulcers or the number with active peptic ulcer, the incidence was slightly lower rather than higher in shift workers, Table 1.

TABLE 1  
*Incidence of Peptic Ulcer Among  
Shift and Night Workers*

| Type of work  | Number of men | % WITH PEPTIC ULCER |        |
|---------------|---------------|---------------------|--------|
|               |               | Total               | Active |
| Regular day   | 3404          | 6.46                | 4.43   |
| Day shifts    | 790           | 6.70                | 3.92   |
| Day and night | 364           | 6.31                | 4.39   |
| Night work    | 313           | 6.30                | 3.51   |
| TOTAL         | 4821          | 6.48                | 4.29   |

$\chi^2$  tests were done to compare "regular day" work with other types.  $P > .05$  in all cases. Data from *Occupational Factors in the Aetiology of Gastric and Duodenal Ulcers With an Estimate of Their Incidence in the General Population*. R. Doll and F. A. Jones, with the assistance of M. M. Buckatzsch; His Majesty's Stationery Office, London, 1951, 96 pp.

By contrast, in Frankfurt, Germany, Duesberg and Weiss<sup>17</sup> compared the incidence of ulcers in different settings, each delineated by a so-called Krankenkasse — a group service of medical insurance. In one grouping (Kasse #2) 40% of the workers were on shift work, complicated by the circumstance that only a quarter of an hour was allotted as a break for a meal. Duesberg and Weiss write: "Those workers on a shift eat their principal meals at home usually at a time which changes from week to week." For comparison with Kasse #2, these authors refer to workers in Kasse groups #8 to #13, consisting mostly of employees working less heavily and not subjected to shift work. In the latter groups, the incidence of ulcers ranged from 0.32 to 0.79%. The peak incidence in Kasse #2 was eight times higher. Unfortunately, the type of "shift work" was not described presumably because major attention was focused on irregular meal times. This interaction of meal times with shift work was emphasized by W. Menzel<sup>44</sup> who subsequently attempted unsuccessfully to communicate with the original authors, and learned that Duesberg had died in the interim. It is interesting in this connection that, by restricting access time to food, Barboriak and Knoblock<sup>4</sup> have reportedly induced gastric lesions in rats.

In any event, one should also consider a report of Bonnevic<sup>5</sup> in Denmark who compared 300 subjects working by day with 600 individuals working by night. The percentage of subjects with ulcers was 5%

for day workers and 15% for night workers. Moreover, Bonnevie points out (personal communication) that differences in incidence should be viewed with the realization that long-term shift workers constitute a selected group, since some individuals (perhaps 25%, in Bonnevie's estimation) "cannot cope with the shift work and show signs of gastric ulcer more often. . ."

Thiis-Evensen<sup>55</sup> found digestive disturbances reported as reasons for absence from work to predominate in shift workers between 1940 and 1948 but no longer during the span from 1949-1956. In interpreting the disappearance of these differences, Menzel<sup>41</sup> refers to intensive preventive measures against the disadvantages of shift work adopted in the fifties.

One may also raise the question whether the conditions associated with World War II may have contributed to these results. Excessive stimulation could lead to ulcers as a pathologic response. However, the timing of the stimulation along the scale of seasons and that of 24 hours, as well as stimulus duration, also may be critical. We, thus, may reconcile a report that the loads of wartime conditions resulted in a remarkable time relation of perforations of ulcers before the air raids began in Scotland during World War II.<sup>32, 33</sup> The possibility remains that the same stimulation may be detrimental at one circadian time but not at another, a point reported for the rat by Ader<sup>1</sup> for the case of ulcers induced by immobilization for six hours. Other perhaps related temporal effects emerge from work by Brady<sup>6, 7</sup> and Brady, Porter, Conrad and Mason<sup>8</sup>; they relate to the duration of stimulation, as elegantly documented also by Rice.<sup>48</sup>

Ultradian rhythms come to mind in this connection, characterizing mammalian time structure. Their importance may be similar to that of the better known circadian rhythms already reported for mitotic activity in the gastrointestinal tract of experimental animals<sup>14</sup> and also for gastric acidity of human beings.<sup>13, 19, 29, 30, 31, 34, 56, 58</sup> Moreover, recent work suggests that rhythms in gastric acidity are endogenous.<sup>42</sup> In any event, in prospective work on human beings and on appropriate models in experimental animals, several broad categories of factors will have to be taken into account, whether one focuses upon ulcer formation or shift work effects more broadly.

First, information is needed on the many factors contributing to the adjustment potential of the individual in response to a given occupational demand. The nature of the physiologic functions involved in a given kind of work probably can be characterized by free-running rhythmic components and nearly ubiquitous polar characteristics, i.e., directedness in schedule change.<sup>2, 37</sup> Other needed information concerns the kinds and intensities of any interacting synchronizers that may determine the outcome of work schedules, influenced, e.g., by meal routines.

Considering the response of organisms to burdens, we first have to map spontaneous rhythms in pertinent variables, such as the adrenal cortical cycle.<sup>22, 26</sup> We also should realize that the response to ACTH by the spontaneously changing adrenal is not only periodic but its periodicities are in antiphase to the spontaneous changes in hormone concentrations. When burdens act at different times they probably involve a periodicity of response, not only by the adrenal cortex but also of superimposed neural structures, such as the limbic system. Even in the absence of any schedule change the response to a burden itself differs drastically as a function of circadian rhythms and probably in response to other rhythms, such as ultradian and circannual ones.

More specifically, in the fifties and early sixties, it was demonstrated in the Chronobiology Laboratories at the University of Minnesota that adrenal cortical responsiveness, *in vitro* and *in vivo*, undergoes a rhythm.<sup>22, 27, 28, 57</sup> Moreover, the timing of this rhythm differs from that of the spontaneous change in adrenal cortical activity, as gauged by the concentration of corticosterone in serum.

The time relations between circadian rhythms in spontaneously changing levels of blood insulin and in the response of rat muscle to insulin also are such that these two rhythms are roughly in antiphase.<sup>20</sup> There are differences in timing, in the same fashion, between the rhythm in pituitary ACTH and the adrenocortical response to ACTH. Furthermore, the overall response of urinary catecholamine excretion to an ethanol load (tested at different circadian times on human volunteers) is high at a circadian time associated with low spontaneous excretion and vice versa.<sup>47</sup>

Work in Florence, Italy, by Tarquini<sup>53</sup> and Cagnoni shows that certain rhythms may be altered in patients with ulcer. The circadian changes in the plasma cortisol of 15 controls were compared by Tarquini et al.<sup>53</sup> with those of eight patients with peptic ulcer verified surgically. For at least one week before the study, the two groups were kept on the same regular schedule of diurnal activity and nocturnal rest. Thereafter, plasma was obtained four times during 24 hours for cortisol determinations. Upon imputation by the fit of a 24-hour cosine curve, only one of the eight ulcer patients had an amplitude-acrophase pair within the 95% probability range of those found for the controls. There was no overlap among the times (point imputations of the individual cortisol acrophases). Accordingly, on the average the group rhythm in plasma cortisol shows an earlier acrophase in ulcer patients as compared to controls.

In another Florentine study by Cagnoni et al, two groups adhering to the same daily activity schedule for two days were sampled. One group consisted of five patients with gastroduodenal ulcer. Another six apparently healthy subjects served as controls. Rectal temperatures were

taken six times during 24 hours. The body temperature rhythm could be described in the group of patients with ulcer by the mean cosinor procedure. It seems worthwhile investigating further whether rhythm alteration could be a factor contributing to the pathogenesis of ulcers. Does circadian and/or ultradian dyschronism augment the chances of ulcer formation only in the presence of loads and as a function of their timing?

According to Dioguardi of Milano, Italy, a disturbance of the circadian rhythm in gastro-intestinal mitoses could be a pathogenetic factor in ulcer formation. In keeping with this line of thought, yet independently, human mitotic rhythms have been studied by Cagnoni and his school. Information on any spontaneous rhythms of the gastrointestinal tract and on those in response to loads may allow us to specify an optimized timing of those loads that shift workers may unavoidably be exposed to. Exposure at the appropriate stage of a circadian (and ultradian?) susceptibility resistance cycle of the gastrointestinal mucosa may then constitute a preventive measure for reducing if not avoiding the chances of ulcer and other possible occupational hazards.

An experimental model for the study of chronobiology in relation not only to a genetically determined blood pressure elevation but also as a codeterminant of gastric ulcerogenesis has been found by Carandente et al in the spontaneously (mesor and amplitude) hypertensive Okamoto rat.<sup>45</sup> Figure 1 aligns the difference in murine ulcerogenesis as a function of controlled circadian state [in rats kept on a regimen of light by day (06<sup>00</sup>-18<sup>00</sup>) and darkness by night] with earlier data on human cases of perforated ulcer published by Illingworth et al.

Moreover, by 1944 Illingworth et al had shown that perforations of human peptic ulcer were more frequent in males. Figure 2 reveals similar findings in the experimental model here recommended for studies of mechanisms potentially contributing to ulcerogenesis, including shift work. However, the coincidence in timing of a peak in perforations of ulcers in human beings active mostly by day and in nocturnally active rats may indicate that different mechanisms may be involved in the two phenomena; (a rhythm in) healing as well as ulcerogenesis may be factors underlying the perforation of an ulcer.

Many problems in a comparative chronopathology remain to be elucidated, including those related to occupational health and safety. So long as some clinical studies must cover necessarily decades and so long as some of the potentially harmful stimuli to be tested must not be applied intentionally to human volunteers, murine models promise to become invaluable to those concerned with occupational and other aspects of health.

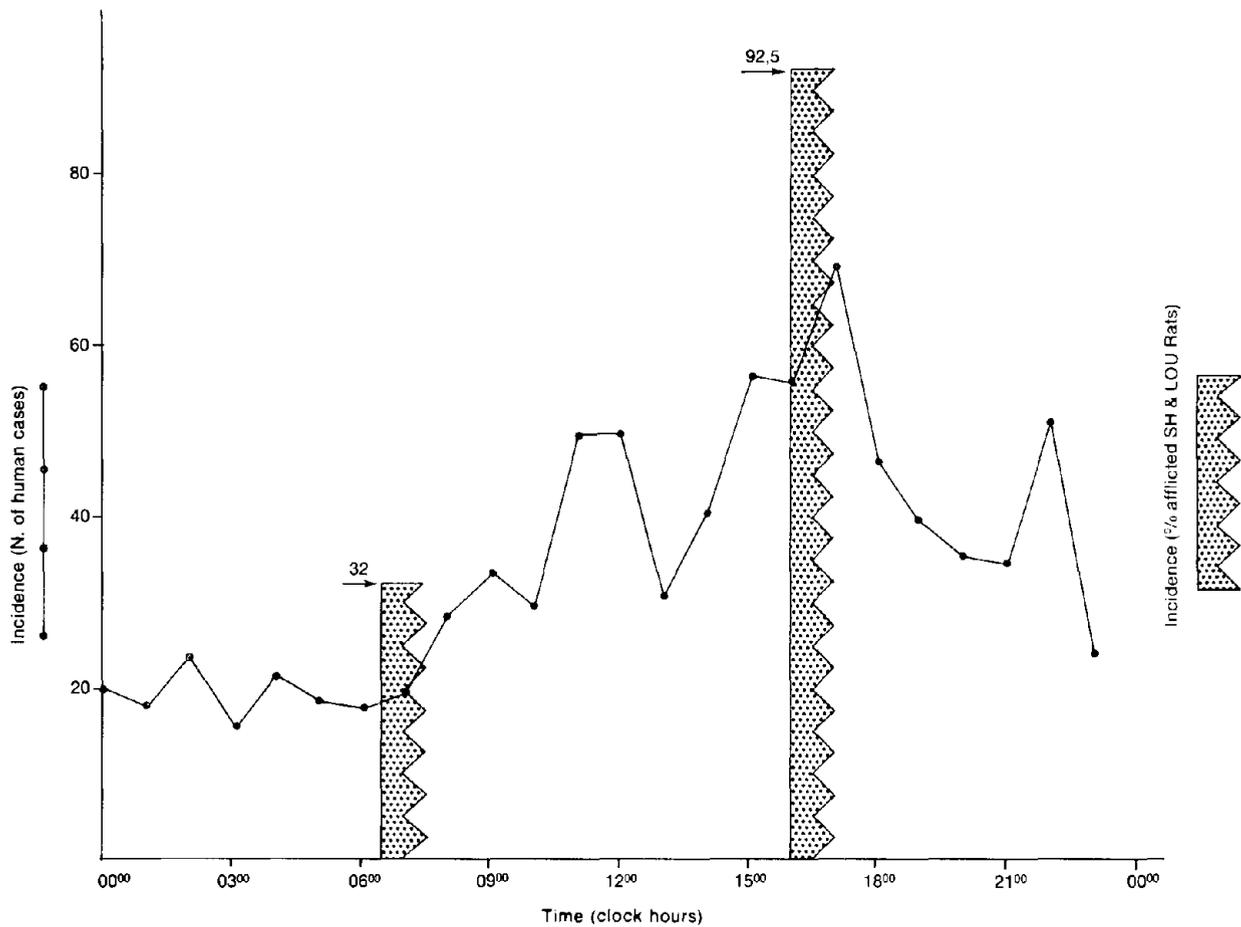


Figure 1. Circadian state and ulcers in human beings and rats.

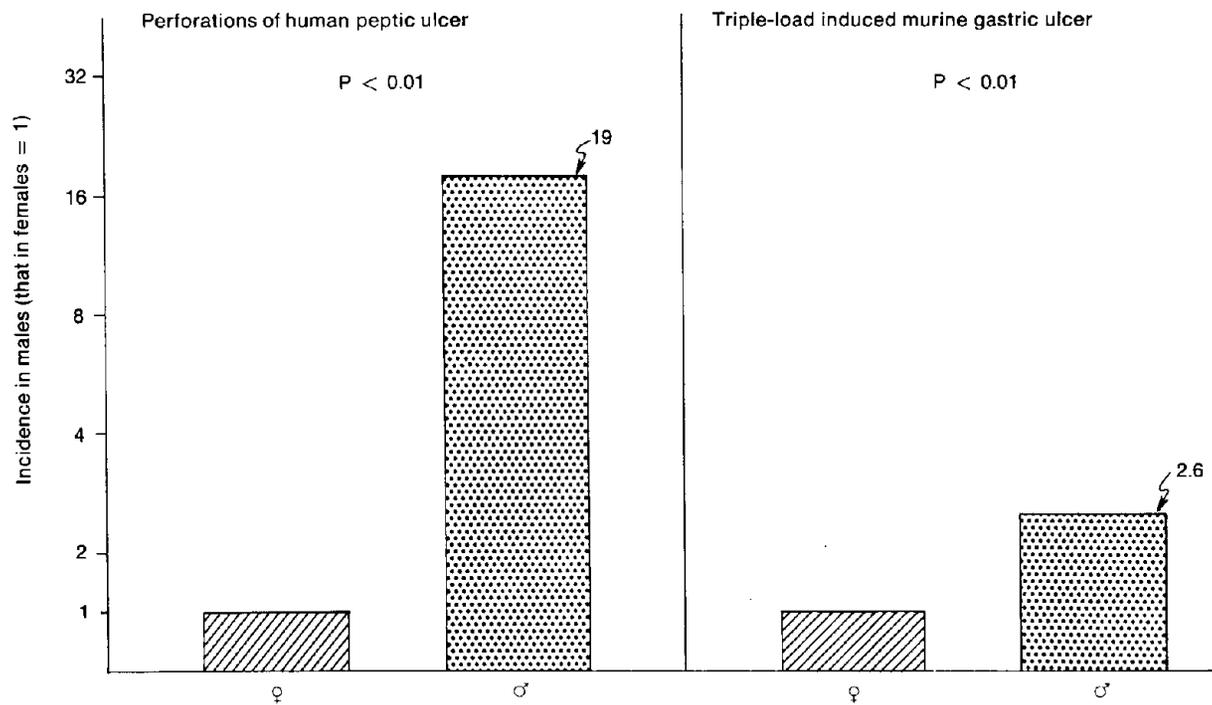


Figure 2. Sex differences in ulcer pathology in human beings (left) and rats (right).

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