Anapryline injection coupled with PMF showed no significant increase of mitosis number.

Thus, PMF stimulates the proliferative activity of the normal and altered liver. A significant role in the realization of this effect belongs to the sympathetic part of the autonomic nervous system.

REFERENCES

1. I. A. Alov, *Outlines of Cell Division Physiology* [in Russian], Moscow, (1964).
2. T. A. Andronova, *Cellular Bases of Regeneration in Mammals* [in Russian], Moscow, (1984).
3. O. V. Volkova and S. B. Tarabrin, *Arkh. Anat.*, **69**, № 1, 5 (1975).
4. P. A. Vunder and V. P. Vunder, *Byull. Eksp. Biol.*, 77, № 1, 109 (1973).
5. V. K. Gurkalo and N. A. Zabezhinskii, *Vestn. Akad. Med. Nauk. SSSR*, № 2, 38 (1978).
6. N. V. Eliseeva and V. V. Neimark, in: *Regeneration of Altered Organs and the Reversibility of Pathological Changes* [in Russian], Gorki (1975).
7. G. N. Kaurova, in: *Liver Regeneration: Regeneration Therapy of Liver Diseases* [in Russian], Gorki, (1985).
8. E. V. Montsevichute-Eringene, *Pat. Fiziol.*, № 4, 71 (1964).
9. V. V. Neimark and N. V. Eliseeva, in: *Regeneration of Altered Organs and the Reversibility of Pathological Changes* [in Russian], Gorki, (1975).
10. I. M. Rodionov, V. N. Yarygin, and A. A. Mukhammedov in: *Immunological and Chemical Desympathization* [in Russian], Moscow (1988).
11. B. A.Sluka, *Arkh. Anat.*, № 9, 64 (1987).
12. L. G. Butterfield and A. H. Neufeld, *Exp. Cell Res.*, **225**, №5, 427 (1977).
13. P. Gool and O. Sand, *Acta Pharmacol.*, **29**, Suppl.4, 25 (1971).
14. R. M. Klein, *Cell Tissue Kinet.*, **213**, № 2, 153 (1980).

Blood Pressure Monitoring according to the "Womb to Tomb" Program with Consideration of the Chronome in Humans

F. Halberg, R. M. Zaslavskaya, G. Cornelissen, E. Halberg, J. Rigo Jr., F. Paulin, Z. Adam, J. S. Rigo, S. Majioni, J. Mello, P. T. Scarpelli, R. Hermida, B. Tarkvini, M. Cagnioni, K. Otsuka, J. Watanabe, O. Quadence, P. Cugini, A. Algren, K. Tamura, and E. Bakken

UDC 616.12−008.331.1−07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 3, pp. 297−301, March, 1993
Original article submitted June 25, 1992

Key Words: *chronome; arterial pressure monitoring*

The development of miniature recorders for arterial pressure (AP), respiration rate (RR), oxygen saturation (O_2), ECG, EEG, gastric juice acidity, body and surface temperature, motor activity, and other functions has made diagnostic medicine more effective. Many new monitoring methods are reserved for solving some special problems, those of chronobiology among them.

Chronobiology is the science of the temporal structure of life. The concepts and facts belonging to this discipline relate to the information containing time series.

Moscow Municipal Clinical Hospital № 60; Semmelveis Medical University, National Institute of Dietetics, Budapest, Hungary; University of Florence, Italy; Wigo University, Spain; Women's Medical College of Tokyo, Japan; Belgian Institute of Aeronautics and Cosmonautics, Brussels; University of Rome, Italy; American Research Association, Washington, USA; Jamanasha Medical College, Japan; Medtronic Instruments, Minneapolis, Minnesota, USA.

0007−4888/93/0003−0325$12.50

TABLE 1. Mean Systolic and Diastolic Pressure (SAP and DAP) Mesors in Women at a High and Low Risk of Developing Mesor Hypertension Monitored at Four Seasons over 24 h with 10 min Intervals*

Season	Group			
	High risk $M \pm SE$	Low Risk $M \pm SE$	Differences	
			t	p
SAP	(n=9)	(n=19)		
Winter	103.3±3.0	109.5±2.3	1.57	0.127
Spring	96.9±1.3	108.1±2.8	2.63	0.014
Summer	97.2±1.4	105.3±2.3	2.37	0.025
Autumn	99.8±1.7	106.6±2.1	2.08	0.047
DAP	(n=6)	(n=5)		
Winter	65.9±1.4	69.7±2.2	1.46	0.170
Spring	64.2±0.8	67.9±3.8	1.04	0.321
Summer	63.8±1.5	67.6±2.9	1.24	0.245
Autumn	63.7±1.4	71.3±2.8	2.58	0.030

Note: Asterisk: risk is explained by family history of high arterial pressure, cardiovascular disease (or black race), obesity, and a note in the examinee's case history about tachycardia or arterial pressure rises.

The usefulness of analyzing serial data structure and interpreting these data from a social medicine viewpoint stem from the possibility of assessing disease risk in healthy subjects and complications in patients by making use of information on rhythm characteristics. This is why monitoring of various physiological functions is highly effective, particularly in the case of AP monitoring. Chronobiologists assess AP excess of deficit as the product of AP and time, which may be demonstrated by the AP monitoring curve square, where this product has neither upper nor lower limits. The introduction of an AP excess hyperbaric index is advisable, this index being presented in mm Hg × h over 24 h and describing the duration of the AP deviation period. New technology helps chronobiologists define the group and individual reference values which may help interpret simple time-specific measurements.

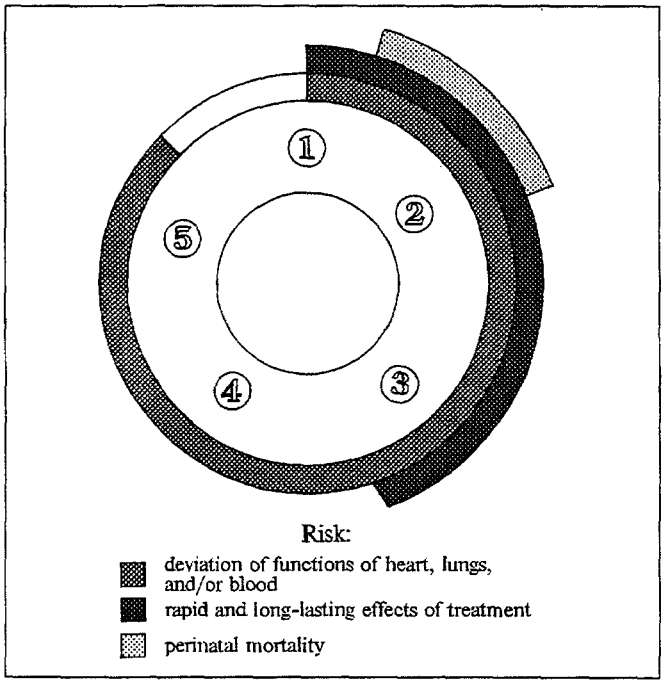

Fig. 1. International study ("womb to tomb" program) of the human AP chronome, the time structure of vital physiological functions, including rhythms of different frequencies, and age-related trends in connection with development, maturation, and aging. Rhythm phases associated with heightened sensitivity and/or risk (chronorisk) may be recognized and utilized, as shown in Fig. 2. Five objects for lowering the risk of developing hypertension: *1*) pregnant woman; *2*) young child; *3*) student; *4*) adult; *5*) elderly person chronome: norm for estimating time-dependent risk of disease (chronorisk).

Standard borders accepted by clinicians as the reference borders for the diagnosis of elevated AP are arbitrarily fixed and based on random measurements. Therefore the AP range approved by WHO (but not chronobiologists!) may be conducive to false positive or false negative diagnoses of benign hypertension in 25 to 48% of the population. The WHO-sanctioned fixed AP range (e.g., 140/90 mm Hg) is chronobiologically unacceptable if we take into consideration the amplitude of AP changes over 24 h in normal subjects. The incorrectness of the universally accepted status quo results both in undesirable side effects of hypotensive therapy and in constant waste of money. Exercise and diet may be the preferred interventions in such cases, and dietetic of other limitations may become chronobiologically more specific.

MATERIALS, METHODS AND RESULTS

Chronobiological studies have shown that the 24-hour mean systolic AP in women with a high and low familial risk of developing high AP, when measured

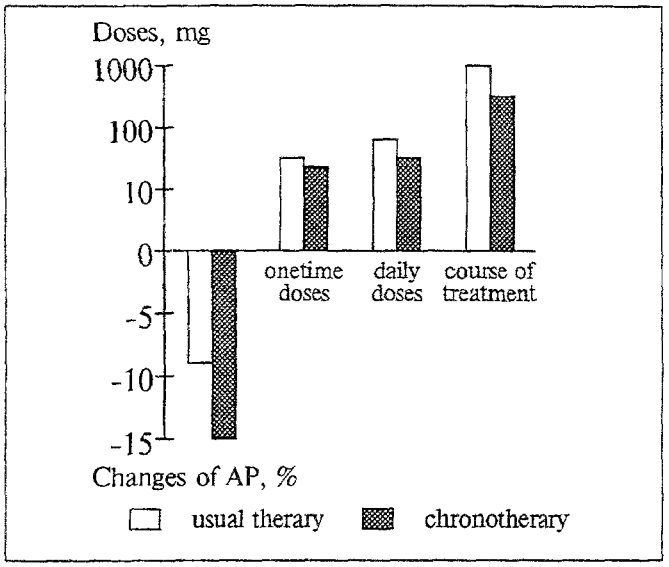

Fig. 2. Chronotherapy and usual propranolol therapy of hypertension mesor. If the daily AP profile is studied and the chronorisk estimated, it becomes possible to administer antihypertensive agents for a certain time, achieving a better and faster therapeutic effect with lower doses of drug.

in the lying position varied over the seasons from 110-105 to 103-97 mm Hg, respectively (Table 1). Differences were also detected in diastolic AP, which varied in various seasons from 68-71 to 64-66 mm Hg, respectively. Julius et al. [3] investigated AP evolutions in 946 healthy subjects aged 18 to 38. An AP higher than 140/90 mm Hg was detected in 124 examinees. Their systolic AP was elevated in childhood and postpubertal age (from 6 to 21). This investigation was valuable in many respects: first, it was prolonged; second, it was started at a relatively young age; third, it involved collection of data for 7 days; and fourth, it proved the usefulness of AP self-measurements twice a day. It is particularly important to detect AP changes in pregnancy, the first weeks of life, and during school hours (Fig. 1). Studies in this field are a priority and international cooperation is desirable, all the more so that it has already yielded encouraging results (Table 2). The "office hypertension" phenomenon merits the attention of chronobiologists. Undersized fetuses and other pregnancy complications are more frequent in women with office hypertension than in those with office normotension. Table 3 shows that 24-hour AP profiles of two groups of examinees are within the normal range on average. Measurements at rest are usually ignored and AP values at rest are not included, which is usually associated with the low level (bathyphase) of the AP circadian rhythm. Differences in labor outcomes are associated with statistically significant

TABLE 2. Assessement of Cardiovascular Risk from Changes in Chronome Structure of Human Arterial Pressure. Circannual Changes in Circadian and Ultradian AP Characteristics in Newborns

A. Circannual changes in circadian mesor and double amplitude reach their peaks mainly in winter

Parameter	Group	M	Mesor 2A	∅	M	Double amplitude	∅
SAP	P−M−	71.7	5.28	−10	5.32	1.72	−359
	P−M+	70.8	5.42	−78	5.84	1.10	−359
	P+M−	73.8	8.30	−120	3.98	1.74	−1
AP_{mean}	P−M−	58.0	4.9	−10	5.14	2.08	−352
	P−M+	57.3	4.94	−66	5.70	0.72	−18
	P+M−	60.0	6.80	−121	4.00	1.46	−14
DAP	P−M−	43.9	3.68	−8	3.94	1.38	−352
	P−M+	43.3	3.18	−58	4.56	1.10	−43
	P+M−	45.0	4.58	−112	2.52	1.56	−23

B. Changes of circadian mesor are more pronounced in newborns with or without a history of high AP in their fathers

Parameter	Double circannual amplitude		
	P-M- n=53	P-M+ n=36	P+M- n=21
SAP	5.2	5.4	8.4
AP_{mean}	5.0	5.0	6.8
DAP	3.6	3.2	4.6
HR	3.6	3.2	8.2

Note: M − circannual mesor; 2A − double circannual amplitude; O − circannual acrophase (360° = 365.25 days; 0°: December, 22.00°°); measurements of the time of all high values. P−M−, P−M+, and P+M− − familial history of high AP: absent (−) or present (+) in fathers (P) or mothers (M); n: number of newborns in a group.

mesor differences. Even small-scale investigations demonstrate differences in the incidence of small-for-date fetuses in the two groups (Table 4). Five out of the 25 women with office hypertension had undersized fetuses as shown by cardiotocography. These results were considered pathological in three out of 25 hypertensive women in comparison with none of 21 normotensive women. Cesarean sections were carried out in two of the 25 hypertensive women and in none of the 21 normotensive patients. A greater body of chronobiological data including labor outcomes should be collected in order to decide which, when, and how pregnant women should be treated.

Chronobiologists advocate the wide use of round-the-clock measurements of human functions. Dynamic AP measurements are best of all carried out with ambulatory automatic devices. Manual measurements can serve the same purpose.

Automatic monitors are available and are most frequently used to measure AP or the heart rate. Chronobiological interpretation of all physiological parameters including real-time prolonged ECG and EEC recordings is a sine qua non in our opinion. There are two conditions chronobiologists insist upon. First, all medical records and serial or single measurements should be time-specific and chronobiologically interpreted in the light of standards variability in time. Second, a chronobiological interpretation can and must be available at minimal cost. From a social medicine viewpoint the price of equipment for AP self-measurements (manual or, preferably, automatic) should be reasonable. Health self-care should become a subject taught in schools. Interpretation of time-dependent measurements of various physiological functions then becomes a component of education in the field of computer-realized chronobiological competence. Such competence helps personal self-care and environmental monitoring.

Regular self-measurements of AP and heart rate in the family setting (so that the measurements may be carried out during sleeping hours as well) and at school in cooperation with the family are essential for progress in attaining this purpose. Schoolchildren and college students can be effectively trained in chronobiology, the training to include the collection and interpretation of the results of measurements of AP, heart rate, and other physiological parameters. Such chronobiological studies have won national regional support in the USA [7] and Italy [8] from government agencies.

There are two approaches to interpreting any series of biological data: 1) determination of the rhythm structure with multiple frequencies and 2) use of primary prevention in time, which is more effective as far as therapeutic measures are concerned, than a reaction to catastrophic events [1,2,6,11-13]. The prevention of infarctions and strokes and the reduction of suffering and costs should outweigh the expenditures for automatic monitors.

Self-measurements carried out and analyzed chronobiologically help the patient and frequently bring about a placebo effect. Analysis of the psychosomatic effects makes it possible to single out the following: the AP of elderly subjects may spontaneously drop by the time when therapy may (or should) be stopped [15]; hence, intermittent replacement of drugs with placebo is advisable for elderly patients. Such switches from treatment to placebo and back to treatment (when necessary) are better controlled by round-the-clock self-measurements or, better still, by ambulatory AP monitoring.

Self-measurements in obstetrics and neonatalogy using manual or automated devices is one more important applications of chronobiological studies. Factors conducive to infant weight loss or to premature labor may be detected earlier, thus allowing for a preventive intervention. Since the time when preterm labor came to be associated with tremendous health service expenditures [18-23], different programs to combat it have been launched. Today neonatal monitoring is limited

TABLE 3. AP in Pregnant Women with Office Hypertension (HT) and Normotension (NT) ($M \pm SE$)

Parameter	2nd trimester		3rd trimester	
	HT	NT	HT	NT
		SAP		
Mesor, mm Hg	116.6±12.5*	100.9±8.2*	119.1±11.0*	104.3±6.9*
MDM, mm Hg	26.9±5.7*	19.3±4.6*	27.7±5.8	23.4±6.3
ΔT, h	$16^{09}\pm3^{17}$	$13^{04}\pm3^{01}$	$13^{32}\pm4^{53}$	$15^{19}\pm4^{11}$
		DAP		
Mesor, mm Hg	71.9±10.0*	62.0±5.4*	74.5±8.2*	64.9±4.4*
MDM, mm Hg	20.7±4.9	18.0±5.2	22.7±7.2	20.9±4.6
ΔT, h	$13^{40}\pm5^{35}$	$14^{15}\pm4^{10}$	$13^{12}\pm5^{09}$	$13^{26}\pm4^{14}$

Note: asterisk – $p<0.01$ (HT or NT); MDM – maximal deviation from mesor.

to the follow-up of the survival of premature infants. We consider that neonatal monitoring should be carried out in line with the "womb to tomb" program. A wealth of information on intensive follow-up of newborns and adults should be stored and analyzed in the form of chronobiological conclusions [6].

AP monitoring of "virtually healthy" subjects may detect many individuals who are at risk of developing hypertension, can pinpoint false negative diagnoses in the presence of a high hypertension risk, and will help prevent its complications. Chronobiological monitoring of patients with benign hypertension will help detect, for example, among pregnant women those in need of treatment (those with false negative diagnoses, that is, with AP values within the normal range). These patients will be treated instead of those who do not need expensive antihypertensive treatment; hence, side effects will be ruled out and the quality of life on the whole improved.These reasons are sufficient to justify the cost of monitoring, to say nothing about the pricelessness of the quality of life.

AP monitoring should be carried out in subjects of all age groups of both sexes, using time-specific ranges for each of these groups. This will help assess both the percent share and the time of AP elevation, as well as AP excess or deficit [11-13]. If it is known that AP excess occurs only at rest or at certain other hours of the day, therapy may be administered at the appropriate times.

More than one hundred scientists from Austria, Bulgaria, France, Germany, Greece, Italy, Spain, and the USA reached a consensus at the Second International Congress of Clinical Chronobiology at Monte Carlo in April, 1990. Later conferences of chronobiologists reiterated their conclusions.

Clinicians in Russia and other CIS countries, working under the guidance of R. M. Zaslavskaya, demonstrated the possibility of improving the antihypertensive effect of beta-blockers and reducing the drug dose ($p<0.05$) merely by compiling round-the-clock AP profiles based on manual measurements and taking the drug 2 h before the circadian peak of AP (Fig. 2). The results obtained with AP may be extrapolated to other fields of chronomedicine.

Chronobiology paves the way toward reducing - possibly toward preventing - suffering thanks to earlier detection of elevated AP and determination of the risks of an AP drop as soon as at childbirth and even *in utero*. Such risk may be detected by monitoring the markers of the rhythm of the physiological parameters or by outpatient AP monitoring or self-measurements.

The consensus reached at Monte Carlo appeals to ethics and to the economy: chronobiology has become a practical discipline thanks to self-care instructions.

TABLE 4. Comparison of Labor Outcomes in Women with Office Hypertension (HT) and Normotension (NT)

Labor outcome	HT (n=25)	NT (n=2)
Preterm labor	1	1
Small for date fetuses*	5	0
Meconium in amniotic fluid	6	3
Abnormal cardiograms**	3	0
Cesarean section	2/5	0

Note: asterisk: p of Fisher's test $=0.023$; two asterisks: $p=0.152$. Two of five cesarean sections were not directly due to high AP.

The consensus presupposes that several problems should be discussed to improve the quality of the health service. They are as follows, as regards elevated AP diagnosis and treatment:

1. The date of examination should be so coded that specific standards of rhythm characteristics may be established.

2. Regular measurements may help detect the precise rhythm of mean values.

3. The rhythm characteristics should be recognized as accurate indicators of changes and used for diagnosis and treatment.

4. Rhythm changes should be regarded as harbingers of a high risk of disease.

5. Rhythms (and the placebo test) should be used to rule out false diagnosis and not to start treatment, as well as to optimize the schedule of treatment when this is necessary.

6. The times of intervention should be noted prospectively together with the results.

7. To optimize introduction of these rules and their wider use in medicine, chronobiological examinations should be carried out in the framework of the "womb to tomb" program. This will help define the pattern of time structure of rhythms and trends in human subjects.

8. It is high time that medical training systems realize the significance of recognizing the phenomena characterized by time structure. This time structure, defined as the chronome, should be depicted in the same way as the genome.

9. The chronome is a genetically programmed and individually developed coded time structure of: 1) multifrequency rhythms; 2) trends of growth development, and maturity; and 3) development as a function of age with marked changes at the beginning and late periods of life. As a direct consequence, the chronorisk may be located between life and death, as a function of the time of vulnerability changes during the course of life. Its accurate evaluation also

depends on the shape of the multifrequency spectrum (or trends) of the rhythm, which changes amidst a multitude of parameters.

REFERENCES

1. F. Halberg, G. Cornelissen, E. Halberg, *et al.*, in: *Chronobiology of Human Blood Pressure. Medtronic Continuing Medical Education Seminars 4th* (1988), p. 242.
2. F. Halberg, E. Halberg, F. Caradente, *et al.*, in: *Proc. Int. Symp. Ambulatory Monitoring, Padua, March 29-30, 1985* (1986), pp. 205-219.
3. S. Julius, K. Jamerson, A. Mejia, *et al.*, *JAMA*, **264**, 354-358 (1990).
4. W. H. Robertson, *Technometrics*, № 2, 103-107 (1960).
5. F. Halberg, G. Cornelissen, and E. Bakken, in: *Chronobiology: Its Role in Clinical Medicine, General Biology, and Agriculture*, Part B, Wiley-Liss, New York (1990), pp. 491-549.
6. E. Halberg, J. Halberg, F. Halberg, *et al., J. Gerontol.*, **36**, 31-33 (1981).
7. A. Ahlgren and F. Halberg, *Cycles of Nature: An Introduction to Biological Rhythms*, National Science Teachers Association, Washington (1990).
8. P. T. Scarpelli, S. Romano, M. Cagnoni, *et al.*,in: *Proc. 2nd Int. Conf. Medico-Social Aspects of Chronobiology, Florence, Oct. 2, 1984* (F. Halberg et al., Eds.) (1986), pp. 345-366.
9. G. E. Brown, *Ann. Int. Med.*, **3**, 1177-1189 (1930).
10. S. C. Mueller and G. E. Brown, *Ibid.*, 1190-1200.
11. F. Halberg, J. I. M. Drayer, G. Cornelissen, and M. O. Weber, *Chronobiology*, **11**, 275-298 (1984).
12. F. Halberg, G. Cornelissen, J. Wu, and P. K. Zachariah, in: *Symp. on Computer-Based Medical Systems, Minneapolis, June 26-27, 1989*, Computer Society Press, Washington, pp. 253-259.
13. P. K. Zachariah, G. Cornelissen, and F. Halberg, in: *Chronobiology: Its Role in Clinical Medicine, General Biology, and Agriculture*, Part A, Wiley-Liss, New York (1990), pp. 243-254.
14. P. T. Scarpelli, S. Romano, R. Livi, et al., in: Chronobiotechnology and Chronobiological Engineering (L. E. Scheving et al., Eds.), Netherlands (1987), pp. 304-309.
15. A. Caruso, S. Ferazzani, S. De Carolis, *et al., VII World Congress of Hypertension in Pregnancy, Perugia, Italy* (1990), p. 30.
16. M. D. Lindheimer and A. I. Katz, *N. Eng. J. Med.*, **313**, 675-680 (1985).
17. J. P. Phelah, *Amer. J. Obstet. Gynec.*, **129**, 397-400 (1977).
18. P. Armstrong, *Brit. J. Hosp. Med.*, Nov., 347-353 (1986).
19. F. G. Cunningham and J. A. Pritchard, *Med. Clin. N. Amer.*, № 68, 505-525 (1984).
20. J. C. Morrison, *Obstet. and Gynecol.*, № 76 (Suppl.), 5S-12S (1990).