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India revisited: a new hospital and center culminating multidecadal cooperation: From cancer chronoradiotherapy to routine cardiovascular chronotheranostics and further joint Indian-US and international BIOCOS research

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Looking back on our January 20–27, 2005 visit to India, it was a whirlwind trip, very rewarding, exciting and also strenuous, in particular for Franz and also for myself, though on a somewhat different level, since I was mainly free of responsibilities. We returned 3 days before I started this note, maybe not long enough to be able to attain a more settled impression and judgment. My main purpose is to give a descriptive report about Franz' effort to bring advances made in mapping chronomes (time structures) into practice in areas with limited resources. In particular, we wish to bring diagnostic and preventive possibilities into the clinical armament by the timely recognition and treatment of otherwise silent yet greatly increased risks of heart and brain attacks.

By prolonged repeated blood pressure measurements we are able to uncover aberrations in what is generally considered a normal range and can treat such alterations to prevent severe vascular disease. Another point is the recognition of the time dependence of treatments. We need to treat at a time when the body is responsive, preferably most so, according to the natural rhythms of our physiologic functions, a special point of interest for pharmacology. I restrain myself from trying to go into too many scientific details. Franz took a CD along, loaded with four different presentations in power point format, making for light luggage, adding evidence on nutrition and the cosmos to a "health watch" for vascular disease prevention and to timed cancer and vascular disease treatment.

There had been a high level of uncertainty about this trip: to go or not to go. The expected physical and mental strain for an 85.5-year-old person could not be overlooked (but really did not matter). Franz decided not to go, notwithstanding firm plans already made, when he was advised that he should sleep on the day after his arrival at midnight. He reconsidered only when it seemed clear that the advice was given out of concern for his health and a program for the day of his arrival was in place. Eventually a satisfactory program was put together, of which the high points of the trip were to be the inauguration of Professor Ram Bahadur (R.B.) Singh's hospital in Moradabad, to be dedicated to Franz (the Halberg Hospital and Research Institute); the possibility of introducing Franz's "Health Watch" to thousands of care providers, actual practitioners of medicine at a convention in Mumbai, and a long-awaited set of lectures in Raipur, invited by Professor Atanu Kumar Pati, the secretary of the Indian Society for Chronobiology, whom Franz had met while the latter was a student in the 1970s. The dedication of the hospital in Moradabad was scheduled for November 26, India's national holiday,

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celebrating the Indian Constitution of Nov. 26, 1950, formulated after India declared its independence from England in 1947. The flight tickets were bought 3 days before departure.

Many years ago Franz had visited India frequently and had carried out various studies there. Most notably, he documented a persisting about-yearly rhythm in the Jamuna River catfish, whether it was kept in continuous light or in continuous darkness and further on a fixed photofraction. At that time, Franz's first wife Erna and daughters Francine and Julia, now both physicians, had accompanied him on trips seeking to establish research projects of interest to both India and the USA, financed by the rupees India owed the US for food shipped from the US to India as famine aid during the Eisenhower administration, the ups and downs of Indian/US relations notwithstanding.

For instance, at an international science congress in Ahmedabad, Franz represented the US, and an otherwise always most friendly colleague from Paris was the French delegate. The Frenchman quickly distanced himself from Franz when Indira Gandhi inaugurated the meeting: she had just returned from Moscow and the French friend correctly anticipated that in her remarks she would call on the US last. Indeed, important countries like Cuba and Sri Lanka were mentioned first. The French colleague did not, however, anticipate that France would be mentioned just before last; he did not know that Franz, as a beau geste to the US, was the only one given a car, a driver and the best hotel. Franz offered a ride to the representative from Russia and does not know whether the French friend took a very long walk or a cab. Even when relations between India and the US were strained, when it came to lodging, transportation or, most importantly, actual cooperation, many Indian friends favored the USA in the clinic, where the 2-year disease-free survival of patients with very advanced cancers of the mouth was doubled by timing treatment (see figure on this page, top left).

As to basic science, in the laboratory, the persistence of about-yearly rhythms in the size of the ovary of the Jamuna river catfish under conditions of controlled lighting and temperature as well as natural conditions was demonstrated. Thus, the built-in nature of these rhythms was documented. In 2005 this finding is a new challenge in view of our discovery of near-transyears that is of unseen years, 55-(rather than 52-) weeks in length in physical-environmental and biological variables. For Minnesotans and Wisconsinites, it is particularly pertinent that in an important variable, the epidemiology of sudden human cardiac death, the fartrans-year—this one discovered earlier by physicists - also found by us as a 15–20-month “year” in many biologic variables, can be more prominent than the harsh change from our hot to cold mid-continental seasons. Over 50 years ago circadian was called Halberg's paranoia and has now become a household word in science and in the Oxford dictionary. Circannual did not fare better originally. Senator Proxmire of neighboring Wisconsin gave it the Golden Fleece Award since he misunderstood that Franz's study dealt with the “love life of the catfish”. These studies, carried out with the late Professor B.R. Seshachar, president of an Indian national science academy, and his associate, the late Professor Bangalore I. Sundararaj, now represent an early model of about-yearly spectral components that may perhaps provide clues for countermeasures to human sudden cardiac death.

I had accompanied Franz on a previous trip 2 years earlier when Professor R.K. Singh (R.K.) invited him for an opening guest lecture at an international symposium at King George Medical College in Lucknow, where we were the houseguests of His Excellency Shri Vishnu Kant Shastri, then governor of the state of Uttar Pradesh. At that time, Franz also delivered a lecture at the annual meeting of the Indian Society of Hypertension and gave grand rounds at the Department of Internal Medicine at King George Medical College. We then visited Professor R.B. Singh in Moradabad, lecturing to the local medical society and to students at a local college of nutrition, and gave invited lectures in Chandigarh, the hometown of Professor of

Radiotherapy emeritus B.D. Gupta (Beedee), and in Amritsar as guests of Professor Adarsh Kumar.

On this occasion in 2005, R.K. Singh in Lucknow had again invited Franz to give a guest lecture at another international symposium, but it was held in mid-February, too late, to our regret, for inclusion in the trip. Again because of the tasks awaiting us at home, we refrained from accepting invitations to Chandigarh and Amritsar on this trip. We regretted further that we could not include a lecture invited by N.K. Singh, a cardiologist and former student of R.B. in Varanasi. Also, we were very sorry to miss the wedding of our young colleague Dr. Sasikumar Sundaram, now a second-year resident in Arkansas, who had monitored the blood pressure of Indian immigrants in California and had detected some cases of blood pressure overswinging among them. His important contributions were emphasized whenever pertinent and hence often in most of the lectures given on this trip.

On January 19, 2005, a bitterly cold day, we left the Minneapolis/St. Paul airport on our way to Amsterdam with the final destination Mumbai, India. We arrived there late at night on the following day, Jan. 20, settled around midnight at the Renaissance Resort Hotel where the congress was to take place. This resort is situated somewhat on the outskirts of Mumbai on a little lake and could easily compete with any of the well known star studded hotels and resorts in the States. Mumbai is the big port city on seven islands on the west coast of India and (as the center of the “Bollywood” film industry) is comparable in the entertainment world with New York, though admittedly falling short. Mumbai was originally named after the region’s patron goddess, Mumba Devi. Mumba is a form of Parvati, the consort of Shiva (Siva), one of Hinduism’s principal gods. The subsequent name “Bombay” developed from the British and Portuguese colonists in the region in the 18th century, either as a corruption of “Mumbai” (the city’s name in the Marathi and Gujarati languages) or as an English corruption of the Portuguese *bom bahia*, “good bay”; the city’s name was officially changed back to Mumbai in 1997.

We felt reasonably rested and relaxed in the morning of January 21. It was a warm, balmy morning, a day without obligation for Franz. But he had requested some activity. R.B. then had arranged a meeting with Professor Gurumukh S. Sainani at the Jaslok Hospital, an about 1.5-h taxi ride from the Resort. After we had been offered a lavish breakfast at the Renaissance Hotel Dr. Mustafa Saif, a young resident from Jaslok Hospital, picked us up and accompanied us to our destination in a cab. He mentioned that he is of Arabic descent: I started to learn then, that the Indian subcontinent over the past centuries and even millennia had been taken over by different invaders, among others by Arabs who brought with them the Islamic faith. The ride in the car gave us a first look at the countryside, the villages we passed and its people in India 2005. To Franz, it was not grossly different, when he tried to make comparisons with his impressions several decades ago on his numerous previous visits here except, may be, for more noticeable building activity here and there, in keeping with India’s growing participation on the world market and with its increasing prosperity.

The Jaslok Hospital, a hybrid name taken from the names of the two physicians who were instrumental in creating this hospital, is a 14–15 story high building alongside a main city street. It is well equipped, with full teaching capacity, on equal grounds with university hospitals and with ties to Stanford University. Professor Sainani, himself a cardiologist, leading us through the different stations, showed us full cardiac care with up-to-date diagnostic, therapeutic and surgical procedures. The facilities seemed to be a bit cramped, but the availability of electron microscopy and of ambulatory blood pressure monitors was impressive. Chronobiologic analyses from Minnesota were offered.

Professor Sainani had his office opposite to the hospital on the same street. We stopped there for a little while, saw the many journals and books edited by our host, and very greatly

appreciated receiving a copy of the electronic version of a textbook of internal medicine edited by Dr. Sainani. Dr. Saif once again accompanied us back to our hotel in a cab. We spent the rest of the day relaxing with red wine and cheese and retired early.

The APICON (Association of Physicians of India CON-gress), attended by thousands of Indian physicians, began on January 22. Franz was invited to talk here today, an opportunity which he appreciated and one of the principal reasons for coming to India to be able to present his “Health Watch”, his fight for a prolonged initial 7-day surveillance of blood pressure in order not to miss a possible life-threatening silent but diagnosable and treatable risk. The presentation went well. The theme was novel to the audience, but well received, although by mid-afternoon the audience had thinned out a bit. Franz probably would have welcomed a bit more questioning afterwards. He engaged in conversation about what he introduced as the pre-metabolic syndrome earlier in Taiwan in November 2004. Many researchers are concerned about the metabolic syndrome, the worldwide spread of hypertension, diabetes, obesity and dyslipidemia.

Time-structurally interpreted blood pressure and heart rate monitoring detects, in the transition from normotension to hypertension, not only an increase in rhythm-adjusted average systolic and diastolic blood pressure, i.e. a MESOR-increase, but preceding both MESOR-hypertension and diabetes, it also detects an earlier increased 24-h swing that is an increased circadian amplitude of blood pressure. Dr. Germaine Cornélissen had found the same blood pressure overswinging in Salvador Sanchez de la Pena’s and Clicerio Gonzalez’ data in glucose intolerance, in a pre-diabetic condition. Thus, harbingers of both pre-hypertension and pre-diabetes can now be diagnosed in general health care practice. I admired Franz’s stamina in piling up evidence for all comers.

Professor R.B. Singh arrived from Moradabad in the late afternoon of January 22, slightly tired, having had to get up very early for the taxi drive to Delhi to catch the plane from there for Mumbai. His daughter Reema and her husband Suryaveer Singh Rao, living in Mumbai, were with him. We had a lovely evening together: Suryaveer invited us to dinner at the hotel’s restaurant which was noticed for its décor, menu and music à la Hyderabad, outstanding on account of the Arabic-Islamic influence. Hyderabad formerly belonged to the wider area under the governance of Bombay, but now for a long time has had its own government.

The next morning, Jan. 23, we went by plane to Raipur. Raipur lies in about the middle of the subcontinent in a vast plain where the sugar cane crop was about to be harvested. Professor Atanu Kumar Pati, India’s leading chronobiologist, was our host. Franz’ first encounter with him was many, many years ago in Varanasi when Professor Pati was a young and upcoming student scientist. He is now a senior professor at the School of Sciences at Pandit Ravishankar Shukla University in Raipur, with focus upon human shift work and biospeleology. Among other contributions, he had found a 24-h rhythm of seepage in the isolation of a cave some distance from Raipur, and we learned more about cave dwellers from him and from the analysis of his data. His research was of interest to me since I had written in my high school questionnaire that my professional goal was to become a speleologist: I eventually became a physician instead. The reunion between Franz and Atanu had almost a touch of sentimentality. Pati had used cosinor calculations in his studies and had embraced chronobiology, which Franz had suggested decades ago in a several hours-long discussion.

Franz’ first talk was to the Alumni Association of the School of Life Sciences. There was the customary introduction and the presentation of flowers, a ceremony in which I was usually included. Franz’ talk here was an introduction to chronomics, the mapping of time structures, certainly pertinent to biospeleologists and human shift-workers alike. His second talk in Raipur was at the MATS University, one of the private universities and colleges, which have sprung

up within the last decade within the general upswing of India's economy and prosperity. The occasion was a very ceremonial event held according to local etiquette. The invitation was in writing and set for a certain time (5:30 pm).

When we entered, a student put a red dot on our fore-heads as a symbol of welcome and friendship accompanied by a few words. We were first guided to a reception room for coat removal and getting acquainted before we were led to the podium several steps above the audience and seated there on wide chairs. We were greeted with introductory words and a presentation of flowers and presents. Among them was the image of the god Ganesa, an obviously cherished symbol frequently seen as the God of friendship and well-wishing, general good will and good wishes for prosperity. Ganesa (also called Ganapati) is pictured with the head of an elephant and a varying number of arms.

According to tradition, Ganesa, the son of Shiva (Siva) and Parvati, stood guard at the door while Parvati bathed. When Shiva approached he was enraged to be kept away by Ganesa and in the ensuing fight cut his head off. Shiva took pity on the grieving Parvati and promised to give Ganesa a new head, the head of the first living creature he encountered, which happened to be an elephant. (Indian mythology thus gives the first description of xenotransplantation).

In a further ceremonial act, before Franz started his talk, he was led to lighten an oil lamp with seven little outlets standing to the right on the podium with some help for this unusual task, an obviously venerated tradition in festive circumstances which I had seen performed by the Governor of the State of Uttar Pradesh at the meeting in Lucknow 2 years earlier before he addressed the participants. The special meaning denotes the sharing of knowledge, protection from ignorance and generally honoring the guest. The students studied biotechnology: Franz discussed rhythms in RNA formation preceding those in DNA formation and filling out a putative mitotic cycle, in which G stages stands for Gaps in our knowledge. The students seemed interested and their questions indicated that they understood the message of timing in molecular biology. The latter discipline can clarify genetic aspects of biological time measurement; but far more importantly, time structure information will prove to be indispensable for a reliable assessment of gene expression more generally.

We stayed overnight at the "Piccadilly" hotel; a large horseshoe shaped building with a large swimming pool in the center, according to name and construction surely a reminder of colonial times. The water level of the pool appeared to be poorly controlled and seemed on the verge to flood the court yard. It was a balmy night and the reflection of the moon shimmered on the water. We enjoyed a lovely relaxing poolside evening meal there with faculty of the School of Life Sciences including the wives and children. Young servers dressed in white suits put whatever we wanted on our plates. It was a romantic night.

The following morning, January 24, also the day of our departure to Delhi, Professor Pati brought us to the Department of Pharmacology of the Medical Faculty of the University for a lecture initiated by the Professor of Pharmacology. We were seated at the head table in the lecture hall with the students already present waiting for us. Unusually for us, female and male students were seated on different sides of the hall, both genders wearing a white uniform (slacks and shirts). The participation of females was almost but not quite equal to the number of males. A guess would be a ratio of 100 males to 80 females. I was not sure whether this should surprise me or not.

Franz' presentation was about chronotherapy; it was well received and applauded. He emphasized the major contribution made by B.D. Gupta in Chandigarh, who by timing treatment had doubled the 2-year disease-free survival rate of patients with very advanced oral cancer. Franz also showed that high blood pressure can greatly vary, by monitoring every half hour for many years, and that treatment can be adjusted to these variations. Hence,

continuous monitoring, which was now possible, was indicated, as in the cases of leading MESOR-hypertensive physicians who had to measure manually. Self-measurement is now much more easily done with automatic instrumentation available at a greatly reduced price to BIOCOS participants.

Our flight from Raipur to Delhi was delayed for 3 h. But the main problem seemed to build-up on arrival in Delhi when Professor R.B. Singh, coming back from Mumbai, was to pick us up in the car of a company of which he is the medical director, to bring all three of us back to Moradabad. He was nowhere in sight. What if we were really stranded here? We had no possibility to communicate with R.B.; we were strangers in an unfamiliar and confusing place and at a loss to make any decision. But Franz finally went back to the main terminal where we should have met him in the first place and found R.B., who probably was just as glad to see us as we were to see him. It was totally dark by then. But without further problems after a 3–4-h ride we arrived safely late after midnight in Moradabad where we stayed overnight in R.B.'s house.

The next morning, Jan. 25, we had a first look at the hospital. R.B. is in the process of building within the complex of his own estate by adding another floor and a suite for the physicians. He is aiming for 25 beds and all the necessary equipment for diagnosis and therapy, including surgery and orthopedics, since he expects his son, now finishing his orthopedic training, to start his practice here. Three beds were already occupied with the patients attended by relatives. What an enormous task! This private hospital is to be inaugurated tomorrow and named the "Halberg Hospital and Research Institute" after Franz. The availability of diagnostic and treatment facilities as listed at the entrance to the hospital are: ultrasonograph, cat scan, X-ray, echocardiogram, Holter Heart Moni, Ambulatory B.P., ECG, C.C.U., I.C.U., Allergy Clinic.

It is impossible to draw comparisons with our conditions here in the USA or Europe and to do justice to conditions in India. Moradabad is a big populated city of about 450,000 people. Availability of electricity is neither general nor regular where a grid exists. Dr. R.B. has his own generator in his complex. Only the center part of the street is mostly asphalted or paved. Animals run freely in the streets, including dogs, cattle and mules, horses. I also saw an elephant. They are mainly used as beasts of burden, pulling carts with whatever has to be transported, fruits, vegetables, bricks, stones and the sugar cane crop, harvested at this time of the year. Throngs of people, the women draped in their colorful saris, crowd the streets during the busy hours of the day. Bicycles, tricycles, motorized three wheelers and handcart pullers and plenty of honking cars, all try to find their way as speedily as possible on the crowded street. But we never saw an accident, though our exposure time was moderate. Apart from travel within cities, on three occasions we traveled by car, each time for several hours, passing and swerving through villages and city streets, very quickly under the circumstances.

Under such conditions like that with a limited infrastructure the establishment of a private chronobiologically oriented hospital can be the more fully appreciated and valued. The inauguration of the Halberg Hospital coincided with Constitution Day, India's national holiday. India declared its independence from the UK in 1947. Three years later, on Jan. 26, 1950, their own constitution was introduced. One of England's lasting gifts for India is the English language. The English constitution was a great influence on Indians hammering out their own, and the English language certainly facilitates the considerable progress India is now making on the world market. The Indus Foundation-USA is a commercial link between the two countries, Canada included, organizing the "Technoamerica" Congress, the American Technology and Trade Mission to India.

We spent part of the morning with the two physicians consulting during their regular office hours, thus seeing patients in R.B.'s clinic. Patients were standing in line. I was told that about

100 patients were triaged as needed and received advice, medication, X-rays or ECG as indicated. All this was done in relatively small rooms with open doors. Privacy was nobody's concern. A young man brought an old man his grandfather?—carrying him on his back to have him seen by the doctor. The day we visited was the 1 day of the week when patients of all ages could come free of charge.

In the early afternoon R.B. brought us to a dental school, and Franz lectured on how dentists can serve preventive medicine while the patient is a captive audience with an open mouth and cannot reply to what the dentist says about preventive blood pressure monitoring. Franz raised the challenge of the very large risks associated with what dentists can detect if they persuade their patients to monitor their blood pressure for 7 days. He had documented the need for action by dentists in Minnesota, in a study with Erwin Schaffer, dean emeritus of the University of Minnesota School of Dentistry and Dr. Frank Raab as thorough researchers. The lecture was well received; Mr. Misra, the owner of the school, provided a generous honorarium, and we were then rushed at breakneck speed to the other end of town for a lecture on chronotherapy for pharmacy students. Franz was again in his element, showing again that hypertension, or more accurately MESOR-hypertension, is not a fixed condition but changes, as shown by half-hourly monitoring for years at a time, with very few gaps. His point was that there is the same need for continuous surveillance in treating blood pressure as is apparent for treating diabetes, and that this is now possible with relatively inexpensive instrumentation for anyone interested in research in regular practice (if so, please contact Dr Germaine Cornélissen, BIOCOS coordinator, at corne001@umn.edu). The purpose of an ongoing project in Minnesota is to obtain even cheaper tools for universal use. This is also a goal of the World Health Organization.

A medical representative hosted our evening meal at a hotel-restaurant, which we remembered from our first trip to Moradabad 2 years earlier. The hospital-associated group had joined us. Franz, sitting beside Dr. J. P. Sharma, President I.M.A. Seohara Branch and Manager of Gyandeep Public School, Seohara, was repeatedly asked by him to stay the upcoming night with him and his wife, also a physician, at their countryside place about 50 km distant from Moradabad. It seemed a little odd to agree to a ~1-h car ride each way, late in the evening after dark, just to have to return the next morning. But we soon learned why. The night was cool and we shivered. This is the northern part of India not too far from the Himalayas, much cooler than Mumbai and Raipur further south. Two thick, fleecy blankets were needed to keep us warm during the night. The shower arrangement, which we encountered also elsewhere a few times, consisted of two faucets at hip height for cold and warm water with the warm water coming from a small gas heater above. Under the faucets an oversized pail with a small container sat on the cement floor. As I was totally unaware how to use this arrangement, I refrained from using it.

In the morning, Dr. Sharma guided us around in what appeared to be a widely spread compound with several buildings, partly unused or under construction. He pointed out the different herbs and vegetables they grew for their own consumption, partly known and partly unknown to us. We were then loaded into the car and brought to our great surprise and still within their private compound to the elementary school they had founded. The children, nicely uniformed and well-behaved, were lined-up in rows in the courtyard, waiting for us. It was Constitution Day, the national holiday and a day to celebrate. Franz was given the honor of raising the Indian flag while the national hymn was sung, and on invitation extemporized an oration. The children gave a little show of which to my great regret we could only attend the first two numbers as Franz thought we had to be on our way to be back on time for the ceremony of the dedication of the Halberg Hospital in Moradabad. Our hosts still wanted to show us their latest initiative to furthering education and bring it into rural areas. They were building a medical college at the outskirts of the town.

The site was (I guessed) about 10 acres, surrounded by a brick wall with teak trees planted along the inside. The brickwork of the building was pretty much completed. Dr. (Mrs.) Meena Sharma (obstetrics and gynecology), who proudly mentioned that her grandmother and her mother had also been physicians, explained on my inquiry that it was not always easy to get money but they apparently could manage. It was the initiative of this physician couple to bring a new college into being. My utter admiration for these civic-minded people! This is another example of India's general economic upswing. The fee for a 1-year course apparently was to be a few thousand rupees (as of 4 March 2005, 1 US \$ = 43.65 Indian rupees).

Back in Moradabad the preparations for the dedication were underway. The ceremony was held in a courtyard at the entrance to the building constituting the family's living quarters. A table was set and rows of chairs placed within the walkway. Some of those in attendance were invited; others just came and watched. R.B. initiated the program. There was the customary flower presentation first, followed by R.B., declaring the opening of the "Halberg Hospital and Research Institute", followed by Franz's address, who emphasized the importance for blood pressure supervision as part of general measures for prevention of heart diseases, especially stroke. Franz hopes that it will be the first hospital to provide automatic 7-day blood pressure and heart rate monitoring for each inpatient, and if the hospital stay is shorter than a week, the monitoring can continue at home. Moreover, he also hopes that as soon as possible, all data can be chronologically interpreted while reference values are being gathered in Minnesota and eventually will be accumulated locally. After Franz's talk, Mr. Masoon Ali Azad, the Imam (chief Muslim cleric) of Moradabad, gave a speech and a blessing. (I was told that Hindus and Muslims get along quite well.) A red ribbon was then cut at the entrance to the hospital. Also the newspaper and photographer were present. It was a beautiful clear day and the sun had warmed-up the otherwise rather chilly air. The Halberg Hospital and Research Institute was a reality.

After lunch, we climbed into a taxi and were on our way to Meerut, a few hours drive on a bumpy road for a meeting with Guru Akhilesh-Ji, also arranged by R.B. The Guru shares with the chronobiologist the common ground of interest in meal timing. The Guru attributes spiritual values and a good way to lose weight if needed to his schedule of meals: no breakfast, only a small amount at noon and a regular good meal in the evening. Franz had done some studies on meal timing. He had found that the same amount of calories taken in the morning may be associated with weight loss while taken in the evening it can be associated with a relative increase in body weight, i.e. a lesser loss than on breakfast-only or an actual weight increase. Usually, other things remaining the same, there is a relative body weight loss on breakfast vs. dinner.

There was a friendly, half-formal discussion in the evening in the general assembly hall about this topic with the Guru sitting cross-legged on a podium with his followers also sitting cross-legged in front of him, who on this evening were rather sparse, and Franz on a chair to the Guru's right. It may have started as an evening prayer meeting; Franz had to wait a while before he got the floor to talk about the results of his studies in regard to the timing of food intake. Guru Akhilesh-Ji was commissioned by His Divine Grace "Yogi Ji", who died 2001 at the age of 96 to be his successor. Yogi Ji based his teaching (the Tap Seva Sumiran series) on Vedic philosophy: "He deduced that elevation of consciousness and attainment of spiritual horizon with a disease-free body can be achieved through TAP (fasting), SEVA (tithing, sharing one-tenth of one's income with others, i.e. through charity) and SUMIRAN (meditation)." We were generously given many books, including one suggesting that food is not the source of energy. The merits of the Guru's principal concern, fasting, are well-documented in the same studies that led Franz to chronobiology in 1949, namely the analysis of adrenocortical function of mice on a diet reduced in calories by 50% with respect to carbohydrates and fat, but containing a full amount of protein, vitamins and minerals. In these studies, Franz had found an increase in

indirectly-assessed adrenocortical function that could have contributed to the longer life and the much reduced breast cancer incidence of the mice on reduced food intake.

We made the rounds of the enclosure, visited numerous buildings, and were invited to supper with the Guru in yet another building. He was seated cross-legged against a wall on what appeared to be a padded table the same height as the table on which we were seated opposite to him on chairs. The delicious meal was mainly vegetarian and was served by his wife, putting small amounts of different foods on our plates and quite frequently replenished. The Guru had to leave early the next morning to fly to Lucknow for a lecture, but Dr Germaine Cornélissen had already analyzed some data he had collected and given to R.B.

We retreated to our quarters and were very pleasantly surprised to see a fire in the fireplace which had warmed-up the room considerably. It was a chilly night outside. The Guru's wife, a lovely spirited woman of 50+ years according to her own statement, had done it and attended to it the following morning also. It was now Jan. 27, and shortly after midnight we were scheduled to leave from Delhi to return to the US. In Taipei (Taiwan) at a conference in November 2004, Franz had met Dr. S.S. Rastogi from Delhi, president of the Indian Society of Hypertension and a good friend of Professor R.B. Singh. The latter had arranged for a lecture by Franz at Shanti Mukund Hospital, where Dr. Rastogi was a consultant. Dr. Rastogi introduced Franz, who lectured on the theme of stroke prevention.

In a happy occurrence before the lecture, Franz had a very short reunion with Professor B.D. Gupta, his friend from Chandigarh, who had come to see him. Franz and Dr. Gupta exchanged a big friendly bear hug such as I rarely see Franz doing. They had done the study together many years ago about the timing of radiation treatment in patients with oral cancer, mentioned in Raipur and again in Moradabad, and had found that the outcome as the 2-year disease-free survival rate was doubled when treatment was given at the time of the highest daily tumor temperature.

I counted that this was Franz' 10th presentation during our weeklong stay in India. He looked pale and somewhat slow in his talk but very much to the point. I thought it might be time to start on our way home. After the lecture, thanks to R.B., who remained in Moradabad, we were introduced to a very dear family. The father, Professor Anshu Sinha, a geologist, just retired from his position in Lucknow as professor and head of a paleobotany institute and vice-president of Earth Systems, considered himself a Himalayanist and had written a detailed big book about the Himalayas, beautifully edited which he showed us and which indeed we greatly admired. The mother was a physician who had to change her position with their move from Lucknow to Delhi. Their physician daughter, a charming young lady, had only recently finished medical school and had just returned from a successful paper presentation in Florence. She obviously was the apple of her parents' eyes and the object of their ambition. She is now trying to attain access to a study program in the USA. They kindly offered to bring us to the airport in New Delhi, saying that they lived nearby. In fact their home was about an hour's drive from the hospital through the city. They invited us there, served a delicious dinner and showered us with gifts until it was time to go to the airport, where they kindly waited to ascertain that we had boarded the plane.

Here I have to enlarge a bit on the custom in India about bringing young people together for marriage. The parents arrange this through newspaper ads. In this case it was Professor R.B. Singh looking for a bride for his son and Professor Sinha, looking for a partner for his daughter who crossed letters, only to find out that R.B. and the girl's mother, Meenashki, had been class mates at Medical School and knew each other. Therefore they rekindled their connection and it was our good fortune to get to know another kind congenial likable family quite apart from the transportation to the airport. I certainly want them as our friends. They brought us first to

their home in the most modern section in the vicinity of the airport where they just had moved into a high-rise building after leaving Lucknow, situated in close neighborhood to the many new expanding buildings of internationally trading companies, another reminder of India's growing importance in the world economy.

Along our way during the last week we had received many presents, several representing the God Ganesa, not the most important in the hierarchy of the Indian gods, as are Shiva and Vishnu, but obviously a very much loved symbol, a visualized metaphor for friendship, welcome and general good will, ("remover of obstacles" according to the Encyclopedia Britannica). Dr. Sinha noted that she had three images of Ganesa in her home, one hanging over the entrance door. Customs, languages, religions, habits and clothing differ, but the same basic human values in all their variations are the same.

Let us hope that Indians will spearhead the transition from single-sample spotchecks in medicine to one of continuous surveillance, and that in this endeavor R.B. Singh's Halberg Hospital and Research Institute in Moradabad, along with Professor R.K. Singh in Lucknow and an extension of the scope of B.D. Gupta's foundation will all contribute to bringing into practice what Indian investigators have already accomplished in research. In basics, we face the challenge of a follow-up on the demonstration of about-yearly rhythms, demonstrated to persist in the catfish under constant conditions of illumination or darkness, albeit with a reduced amplitude. In the clinic, we can try to serve B.D.'s, R.B.'s and R.K.'s trust.

Joint research with Professor Atanu Kumar Pati in Raipur, his fine team locally and his Indian Society for Chronobiology, is to be both basic and applied. In particular, his studies of hypogean loaches living in the constant darkness of the subterranean Kotumsar cave and of their epigean ancestors inhabiting the fast flowing river outside the cave offer an elegant model for the study of competing photic and non-photoc influences on the time structure of physiological variables such as locomotor activity. Other joint research planned with Professor Pati involves blood pressure and heart rate monitoring around the clock, and along the weeks on shift-workers. It may serve to recognize and treat, and thus to minimize the occupational health hazards among shift-workers, to maximize their performance and augment productivity, as he aims to do with us. A mix of basic and applied science that brought us to Moradabad may flourish by extension also elsewhere in India. We remain grateful to R.B. Singh for fostering developments everywhere around the globe for a health and science care that does not "fly blind".

Diagnoses based on spotchecks and treatments by clock-hour, if not by convenience and based on pharmacokinetics rather than chronopharmacodynamics, are a great advance. Nonetheless, in so doing, most of the time, as a journal editor put it, without monitoring we are "flying blind" as to whether the treatment really does all what it should do, rather than the opposite when alleged pseudochronotherapy in the evening brings about the high-risk condition of blood pressure overswinging.

Countries with limited resources that cannot afford the care of severe overt disease, such as coronary artery bypass grafting, may set an example for dealing with the uninsured in developing areas. Monitoring the safety of the circulation as a routine endeavor, as was done by Professor Kuniaki Otsuka in Tokyo and has been initiated in Urausu, Japan, as implemented in Brno, Czech Republic, and in the Moradabad hospital may set an example for the world, including Minnesota, if only the implications of the two figures on top of page 2 of this article are implemented.

Research on about-yearly changes, started in India (see figures on next page), and originally deemed by U.S. tax-payer watchdogs as useless (as they might also have deemed Einstein's relativity theory were it not indispensable for global positioning), interest in about-yearly and longer rhythms is now being extended in relation to extra-yearly aspects of human sudden

cardiac death. This work has led to important geographic differences in patterns of death possibly relating to geomagnetics as a proxy if not cause, a point yet to be clarified.

As a more immediate application of Indian contributions, today one could provide the treatment of certain cancers when it acts best, preferably by measuring tumor temperature as a marker of timing. Also today, one can treat the risks of vascular disease rather than only the actual illness, as can now be implemented with time structural analyses at the Halberg Hospital and Research Institute in Moradabad. A spotcheck medicine can thus be changed to one based on time series that allows us to “fly with open eyes”. This preventive orientation is particularly pertinent to areas with limited resources, wherever, irrespective of geography, people are uninsured and/or otherwise barred from modern health care. Conceivably, the implications of research on about- and extra-yearly changes in the catfish as these may relate to human sudden cardiac death, may also bear fruit (see figures on next page).

1. .
Halberg Hospital and Research Institute in Moradabad, India

2. .
Inauguration ceremony and blessing by Imam

3. .
Cutting of ribbon

CHRONORADIO THERAPY (Rx)

4. .

Radiotherapy at time of peak tumor temperature is associated with fastest tumor regression and highest 2-year disease-free survival Study by BD Gupta and F Halberg

Endogenicity Suggested by Rhythm Persistence with Phase-Drift (Free-Run?)

5..

Abnormal blood pressure variability and heart rate variability, detected within the physiological range, is associated with cardiovascular disease risk that can be reduced by treatment timed to restore healthy dynamics Study by K Otsuka, G Cornélissen and F Halberg

6. .

Reduction of circannual amplitude in constant lighting conditions demonstrated by parameter tests

Sudden Cardiac Deaths in Minnesota (1999-2003)

(1-way ANOVA: 12 classes: $F=1.134$, $P=0.330$; 6 classes: $F=0.903$, $P=0.478$;
cosinor: $2A = 0.052/\text{day}$, $P=0.171$)

Sudden Cardiac Deaths in Minnesota (1999-2003)

(1-way ANOVA: 12 classes: $F=1.462$, $P=0.139$; 6 classes: $F=2.282$, $P=0.044$;
cosinor: $2A = 0.084/\text{day}$, $P=0.014$)

7. .

The incidence of sudden cardiac deaths in Minnesota follows an about 1.39-year (right) rather than a calendar year (left) pattern. From G Cornélissen, F Halberg et al. (submitted)