Chronobiology International, Vol. 7, No. 3, pp. 179–186, 1990
Printed in Great Britain

0742-0528/90 $3.00 + 0.00
Pergamon Press plc
International Society of Chronobiology

SOURCES OF THOUGHTS

FROM TEMPERATURE REGULATION TO RHYTHM RESEARCH

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Key words—Body temperature, daily variations, circadian rhythms, history of research.

At the time when I joined the Physiological Institute at the University of Göttingen in 1938, the director Hermann Rein was interested in circulation and temperature regulation. He asked me to study mechanisms of cold defence in humans, with emphasis on convective heat transfer. After preliminary experiments dealing with temperature effects on blood vessels *in vitro* (1), I started measuring heat loss from the extremities in ice cold water, together with rectal and skin temperatures (2). I was my own subject, and my wife assisted me as a technician, taking care of the recording instruments. As the experiments grew longer and eventually covered a full day, I not only noticed the well-known 24-hr variation in rectal temperature but also a systematic and quite large variation in heat loss not previously described (3). To understand the cause of this rhythm, I checked the textbooks of physiology available at that time. The monograph of Rein (4) mentioned the "Tagesgang" (daily trend) of rectal temperature in one sentence, accompanied by a curve from Benedict and Snell (5), without giving any explanation. Rosemann (6) spent a full paragraph on the phenomenon. He concluded that "the daily variation cannot be attributed solely to the effects of ingestion and muscular work" (my translation from German), referring to the observations that the rhythm persisted during bedrest and starvation (7), and could not be inverted by sleeping during the daytime and working at night (8, 9). Thirdly, I read Fulton's 15th edition of Howell's famous textbook (10) and learned that "this daily variation shows individual peculiarities that depend largely upon the manner of living, time of meals, etc.". In *Starling's Principles of Human Physiology*, edited by Evans (11), I found: "With these diurnal changes in temperature are associated parallel oscillations in the rate of metabolism... They are probably determined by the changes in the movement and tension of the muscles occurring during the working hours". [For references to early demonstrations of the rhythm in body temperature see (12).]

These remarks of four well known physiologists left me with quite some uncertainty. Hence I went to the publications of experts who had studied the problem experimentally. Among those was Arthur Jores, Professor of Internal Medicine at the University of Hamburg, who had written one of the first review articles on the subject (13). In view of those studies which failed

Jürgen Aschoff was born in Freiburg/Br. on 25 January, 1913, as the fifth child of the Pathologist Ludwig Aschoff and his wife Clara née Dieterichs. He was a late-comer, and remained being a late-developer all his life. Both parents were of North German origin, and Prussian sprinklings are recognizable in Jürgen's imprint from the Black Forest. Spoiled by three older sisters, and sometimes beaten by a much admired, skilful brother, he was a lively but timid child, eventually gaining some vigour when he became a boy scout. At the humanistic gymnasium he received only medium or lower marks, especially in Mathematics and Latin, but was second-best in sports. Once, he tried to grow cacti, but otherwise his biological interests were minimal. For three years he practised the violin, with modest success. For want of an inclination to any specific profession, he began studying Medicine in 1931 in Bonn, where he joined the "Burschenschaft Alemannia", and obtained his M.D. in Freiburg in 1938. Much of his time he spent reading novels, Joseph Conrad being his favourite author.

to demonstrate an inversion of the rhythm by night work, and of reports from journeys on ships during which the rhythm remained fixed to local time (14, 15), he concluded: "These investigations leave no doubt that the rhythm of temperature does not depend on the way of living, and is coupled to the time of day" (my translation). In a later article, Jores (16) stated more explicitly that "the dependence of the periodicity upon local time ("Ortszeit") argues unambiguously for an external control" (my translation). A similar conclusion was drawn by Völker (17) on the basis of his own inversion experiments; although he was inclined to believe in the hypothesis of an "internal rhythm", he still insisted that the rhythm was strongly coupled to local time. This is somewhat surprising because Völker himself had seen partial shifts of the rhythm in subjects who had reversed their way of living in the laboratory, and in spite of his knowledge of publications in which substantial shifts had been described. Among the authors to whom Völker refers are Toulouse and Piéron (18) who had studied the rhythm of body temperature in nurses. They noticed that, after 24 days of night work, "l'inversion n'est pas encore complètement realisée, mais elle nettement esquisée; elle se produit très lentement, par retard progressif du maximum, puis de minimum". ("... the inversion has not yet been fully realized, but it is clearly outlined; it takes place very slowly by a progressive delay of the maximum, then the minimum"). The authors conclude: "Ce n'est pas la periodicité cosmique du jour et de la nuit qui détermine le rythme nycthéméral... D'autre part, il n'y a pas dans cette oscillation une périodicité essentielle tenant à la nature même de l'organism". ("It is not the cosmic periodicity of day and night which determines the nycthemeral rhythm... On the other hand, there is no essential periodicity in this oscillation depending on the very nature of the organism"). Völker also refers to Lindhard (19) who, in 1907, participated in an expedition to Greenland. During the àrctic winter days with permanent darkness he persuaded his camp fellows to shift their sleep–wake cycle (and their watches) by 12 hr, and he saw, in 14 out of 28 subjects, a more or less complete inversion of the rhythm within 5–6 days. Lindhard criticized the apparent negative results of earlier inversion experiments with the remark: "One cannot disconnect the individual from society; as long as the latter follows a fixed routine, the single individual will, consciously or unconsciously, tend towards the same mode of life." Lindhard's interpretation of his results was: "All of them tend to show that the curve of temperature variations is determined by work and mode of living, that the astronomical division of day and night is without importance in this regard, and that an inherited form is consequently out of the question, a mysterious periodicity even more so."

In essence then, what I did find in the medical literature was a discussion on whether or not the rhythm depends on the way of living. The majority of authors denied such effects and gave much weight to observations which suggested that the rhythm is "ortszeitgebunden" (coupled to local time) and hence must be controlled by an unknown (cosmic?) factor. The pediatrician De Rudder, to whom we owe an excellent monograph on Biometeorology (20) summarized this view in the following sentence (21): "The existence of statistical daily rhythms, and the non-existence of small constant deviations from 24 hr in the duration of the rhythm in individuals ... is intelligible only by assuming external factors" (my translation). All of these authors, except Jores (13), rarely referred to experiments made with animals or plants, and in almost none of the publications was there an explicit outline of the hypothesis that the rhythms could primarily be based on an endogenous periodic process, not to speak of considerations how this hypothesis could be tested rigorously. It did not take me long to discover that this was the major issue of discussions among the biologists. I also soon realized that there was one, and only one, strong argument to defend the endogenous nature of the rhythm: If in constant conditions the rhythm continued with a period deviating from 24 hr, it could not be controlled by external factors.

When I began reading publications from zoologists, I was surprised to notice how many emphasized that, in conditions which they considered to be "constant", the rhythm persisted with a period of exactly 24 hr; e.g. in the activity of crickets (22), in the chromatophores of crustaceans (23), in the eclosion and eye pigments of moths (24, 25), and in the activity of voles (26). A few reports suggested deviations of the period from 24 hr, e.g. in the activity of canaries (27), mice (28), and bramblings (29), but the temporary and inconsistent shifts had little convincing power. The hypothesis of an exogenous control of the rhythm, persistently advanced by F.A. Brown, was initially also based on Brown's early observations that "organisms in constant conditions may retain unaltered phase relationship with the external physical cycles even for periods of months" (30). [For a critical discussion of Brown's hypothesis, and its modifications over the years, see (31).]

More striking were data that indicated a pattern which now would be called a "free-running" rhythm, and which convinced the authors of an endogenous rhythmicity. It might be of interest to those who are entering the field nowadays, for me to add a few quotations in chronological order. Already in 1926, on the basis of activity records obtained with white-footed mice in continuous darkness (DD), Johnson (32) suggested that "possibly the mice have an innate tendency for an activity rhythm". Eleven years later, Hemmingsen and Krarup (33) observed, in continuous light (LL), a delay in the activity rhythm of rats by 2 hr per day. Their conclusion was: "In our opinion this phenomenon is to be interpreted as an inherent 24 hour rhythm which, owing to the depressing influence of light, is delayed so long as it is possible for the animal to suppress it. It is as if the rat organism wishes to store the activity for a coming dark period, but as no such period comes, it cannot suppress the rhythmic 24 hours activity more than about two hours". At the same time, Kalmus (34) and Bünning (35) had observed that, in the fruit fly, the rhythm of eclosion persisted in DD with periods deviating from 24 hr, even if the pupae had been raised in DD and were illuminated only once. In a remarkable overview, Kalmus (36) pointed out that the "Eigenfrequenz" of the eclosion rhythm in these DD-raised flies gives evidence of an endogenous rhythm which rests on a genetic heritage. Shortly thereafter, Johnson (37) published new data which showed that his mice had a period of 24.6 hr in dim LL, and a period of about 25.6 hr in brighter LL [cf. Fig.1 in (38)]. His findings forced him to conclude: "This animal has an exceptionally substantial and durable self-winding and self-regulating physiological clock, the mechanism of which remains to be worked out." Johnson's results were confirmed in the dwarf mouse by Osborn (39) who found a persistence "on schedule" in DD, but a lag of about 2 hr per day in the onset of activity in LL. Next comes Barden (40) who worked with lizards: "The tendency of the lizards to become active earlier every day which occurred frequently in constant light, is in direct contrast to the daily delay in time of activity found by Johnson for *Peromyscus*, the white-footed mouse." Finally, Calhoun (41) ought to be mentioned. He described for the cotton rat *Sigmodon hispidus* "a shortening of the 24-hour cycle by 20 minutes each day while in continuous darkness", and a "shifting of the peak of activity to a later time in continuous light with an average shift of 30 minutes each day".

From today's point of view one could think that some of the results mentioned in the foregoing paragraph should have been sufficient to cause researchers to abandon the idea that the rhythm was exclusively controlled by external (unknown) factors, and to take the endogenous origin for granted. However, this was obviously not the case in 1949 when I decided to find out for myself whether, in mice kept in constant conditions, the period of the activity rhythm deviated from 24 hr [cf. the selection of references made in (42) and (43)]. That the debate of external vs internal control was still raging is reflected in the contributions to the 3rd Conference of the "Internationale Gesellschaft für biologische Rhythmusforschung" which took place in Hamburg in the same year (44). In his opening address, Jores considered it most likely that the rhythms were controlled by external factors coupled to the alternation of day and night, and in only one out of 30 lectures were data presented that today would be interpreted as suggesting a free-running rhythm (45). Four years later, when the Conference of the Society was held at Basel (46), the hypothesis of external control was still in vogue. Its main opponent was Erwin Bünning; the very first sentence of his abstract (47) states that in the past decades the endogenous component of many daily periodic processes in plants had clearly been demonstrated. In my own contribution to the Conference (48) I pointed out that, after the removal of zeitgebers, an *endogenous* rhythm should persist with a period deviating from 24 hr, and I illustrated this by presenting just-collected data on free-running rhythms in white mice (49) and bullfinches (50). I also was saucy enough to conclude from my few observations that in night-active animals the period is longer in LL than in DD while the opposite occurs in day-active animals. Finally I pointed out that zeitgebers of various modalities could compete with each other, and that periodic (restricted) feeding could overrule a LD-zeitgeber of low amplitude. Here I was referring to Stauber (51) who had studied the asexual reproductive periodicity of *Plasmodium cathemerium* in canaries.

It was at the Basel Conference that I met Bünning for the first time. He encouraged me to continue my experiments with animals, although, to his opinion, the botanists had long ago and definitely answered my main question. Indeed, the documentation of free-running rhythms in plants preceded that in animals (34, 35) by 103 years. In 1832, De Candolle (52) summarized the results which he had obtained with *Mimosa*, in the following sentence: "Lorsque j'ai exposé des sensitives à une lumière continue, elles ont eu, comme dans l'état ordinaire des choses, des alternatives de sommeil et de réveil; mais chacune des périodes était un peu plus courte qu'á l'ordinaire. L'accélération a été sur divers pieds d'une heure et demie ou de deux heures par jour.". ("When I exposed sensitives to continuous light they had, as in normal conditions, alternations of sleep and wakefulness; but each of the periods was a little shorter than usual. In different blades the acceleration amounted to one and a half or two hours per day."). Three decades later, Sachs (53) observed the persistence of the rhythm in *Albizzia*, with periods shorter than 24 hr in LL, and longer than 24 hr in DD. His conclusion was: "It follows that the alternation of light and dark is not the cause of the periodic movements, although it determines its measure of time. The speed of the periodic movements differs in darkness or in continuous light from that under natural conditions" (my translation from the German). In passing over important contributions from other botanists such as Pfeffer (54) and Kleinhoonte (55), I am once more referring to Bünning who wrote in 1932 (i.e. 100 years after De Candolle): "I see no reason any more to doubt the autonomous character of the movements that occur at constant temperature in darkness" [my translation from (56)].

Meanwhile the reader must have noticed that, at the outset of my research in rhythms, I had to do a lot of reading. At that time this was no easy task. With the notable exception of Welsh (57), Kalmus (58), and Calhoun (59) there were hardly any review articles, and it was difficult to find signposts to the history of the field. [Remember: it was not until 1960 that De Mairan's (60) initiating role was pointed out to us by Bünning (61), and only in 1974 (62) that we learned of Virey (63) who first used the term "l'horloge vivante".] But even the most recent literature was hard to get at in postwar Germany. Furthermore, I had no one to speak to. Everybody else in the Physiological Institute at Göttingen was engaged in using sophisticated instruments to measure bloodflow in dogs, and my friends wondered what I was doing with white mice, recording their activity on a slowly moving smoked kymograph [cf. Fig.2 in (64)]. Much do I owe to the most impressive, liberal and versatile personality of Hermann Rein (65, 66) who inspired his pupils as a passionate teacher and skilful experimenter, and who, as importantly, gave us all opportunities to find our own way in science. My fate as a "lone wolf" changed profoundly when, in 1954, I came in close contact with Gustav Kramer (67) who, a short while earlier had discovered the sun compass orientation in birds (68), and with Erich von Holst (69) from whom I learned a lot about the coupling of oscillators and "relative coordination" (70). It is due to the interest that these two outstanding scientists took in my

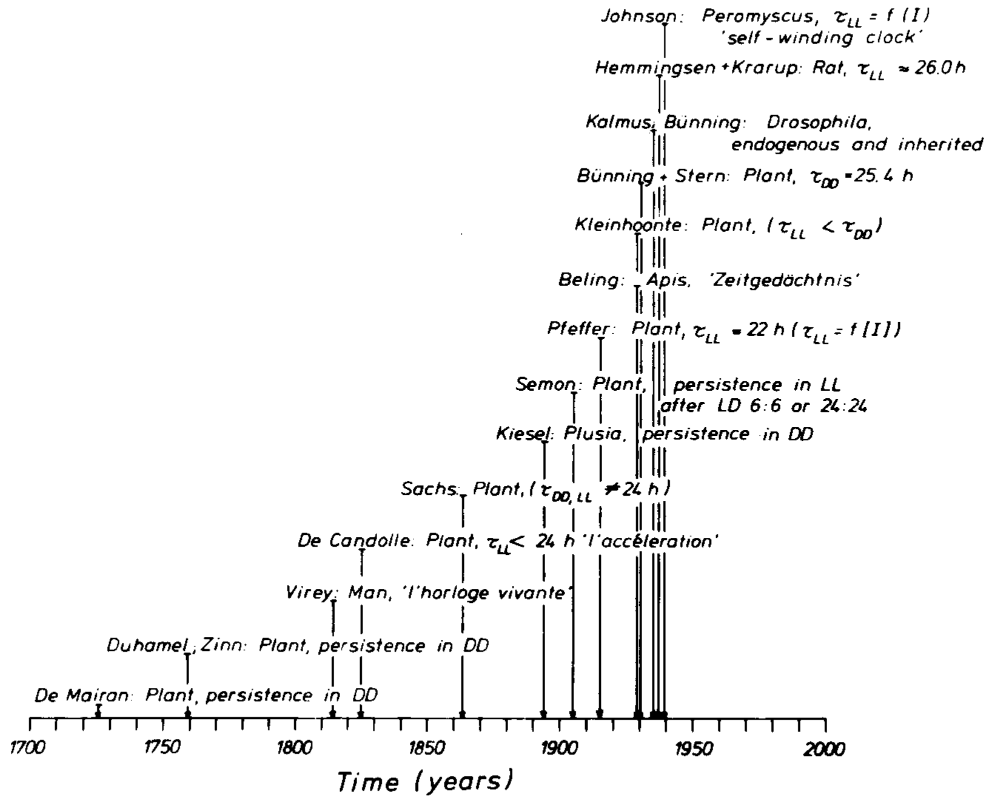

Figure 1. Major discoveries in rhythm research up to the early forties. Symbols: LL, continuous light; DD, continuous darkness; τ, mean circadian period; I, intensity of illumination. References in chronological order: (60, 75, 76, 63, 52, 53, 77, 78, 54, 79, 55, 80, 34, 35, 33, 37). [Reproduced from (38)].

work that, in 1958, I became a member of the Max-Planck-Institut für Verhaltensphysiologie which had just got new buildings at Seewiesen in Southern Bavaria. It was a striking experience to change from (medical oriented) physiology to biology at large with its (as I felt it) much wider horizon, and to make friends with Konrad Lorenz (71) who together with von Holst made Seewiesen a Mecca for the ethologists (72). In the same year, I made my first trip to the U.S.A. where I met, among others, with Woody Hastings (then at Urbana) Curt P. Richter, and Colin Pittendrigh (then at Princeton). This adventure opened to me a new avenue which lead straight into Cold Spring Harbor (73).

In looking back over 260 years of rhythm research that began with De Mairan (60), one might wonder why progress has been so slow (as was envisaged by that researcher). However, if one draws the major discoveries in the field on top of each other as a function of time (Fig. 1), an exponential curve can be fitted to the data which indicates a doubling time in our knowledge similar to that found for biology at large (74). In other words: we have been neither unusually fast nor slow. It seems to me that the history of the search for the biological clock offers a unique opportunity to understand some of the rules by which science proceeds, and in particular to become aware of the traps which are set for us on our way. From wrong tracks as much as from successful attempts we can learn that what we need in science is (apart from having ideas) the courage to speculate, even if wildly, but on the other hand to be continuously on one's guard against drawing premature conclusions based on too few data [as I did by fabricating a "rule"—compare (49) with (81)] or in neglect of an alternative interpretation of our results [compare the 2-oscillator explanation of human "internal desynchronization" given in (82) with the model offered in (83)]. As was recently outlined by Enright (84): "One of the important and rarely discussed stresses inherent in the activities of scientists is the conflict between the imaginative, creative impulse that underlies the formulation of interesting hypotheses, and the cold, hard skepticism that is required in testing hypotheses rigorously". From these two ingredients, it is only skepticism with which one can tutor oneself. It would probably not have taken me such a long time to learn this lesson if I had read earlier what Charles Darwin wrote to Anton Dohrn on 4 January, 1870 (85): "As Demosthenes said, 'action, action, action' was the soul of eloquence, so is caution almost the soul of science".

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