Curt Richter

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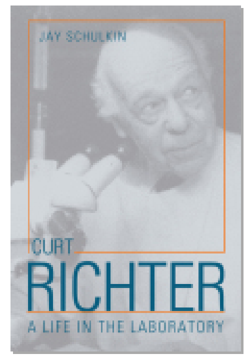

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CHAPTER 2

Biological Clocks and Spontaneous Behaviors

Curt Richter commented on his own youthful tinkering that he "spent a lot of time working on locks and clocks—taking them apart and putting them back together again" (Richter 1985, p. 359). Richter began his research career by studying cyclic behavior and what many called "spontaneous behaviors." Richter's career began with the clocks and ended with the clocks. They were his first scientific love and a lasting romance.

A romantic vision of nature coupled with an engineering perspective on design and adaptation permeated Richter's work on biological clocks and their role in regulatory physiology. Moreover, he saw behavior not as an appendage or aberration, but as an essential ingredient of physiological regulation. Clocks help generate the behaviors animals use to perform activities vital for their survival. Clocks, in Richter's view, are not subject to external perturbation, but trigger a variety of adaptive behaviors—an engineering principle that allows behavioral flexibility and problem solving.

Richter understood biological clocks as fundamental to the organization of behavior and physiological adaptation. In fact, before Richter there were limited experimental contexts for inquiry into biological clocks and their role in the regulation of behavior, though there had been some discussion of them, notably by Johnson (1926). The role of clocks in regulating behavior and physiology, particularly in mammals, would not be fully understood for decades (Rusak and Zucker 1979; Rosenwasser and Adler 1986).

PSYCHOLOGY AS SCIENCE

The field of psychology was new and searching for legitimacy when Richter first encountered it. It had links to two different historical traditions: (1) the rationalism of Descartes (and modern rationalism), and (2) Hume and modern empiricism. Kant and other forerunners of modern cognitive science tried to synthesize the two traditions. Before the search for the legitimacy of knowledge became embedded in modern epistemology, there was the sound, commonsense psychology of Aristotle and other classical writers about the human condition and its wants and desires.

The intellectual climate in which Richter found himself at the start of his career was rooted in the work of Darwin and William James. The influence of Darwinism was enormous. Despite the rejection of Darwin by James's biology professor, Louis Agassiz, at Harvard, (S. J. Gould 2002), William James embraced the biological perspective that was revolutionizing the sciences, and he incorporated this perspective into his conception of psychology. *The Principles of Psychology* (James 1890/1952) remains one of the most important books in psychology; few textbooks have had such lasting allure. James's pragmatism was fused to his functionalism: What were the functions of a set of behaviors? For James, psychological events were to be understood partly within the context of biological adaptation (James 1890/1952). The same approach would pervade Richter's work.

The goal of the science of psychology, however, was the continued realization of science—positive knowledge. Recall that during this period university philosophy and psychology departments were not separate. Psychology, as James understood it, was the study of the mind. But, again, the mind was not something ethereal; it was functional. For James, the subcomponents of the machinery of the mind, such as attention, were linked to the degree of information that could be processed (James 1890/1952). The emotions, for James and Darwin, evolved as aids to problem solving, which was the basis of functional psychology and was biologically based (Darwin 1872/1998).

One dominant issue for those thinking about the study of behavior was what constituted a real science of psychology. The so-called Subjective school (Titchener 1929/1972) concerned itself primarily with introspection. The issue of introspection was suspect and forbidden for Watson. "Objectivism," as behaviorism was sometimes called early on, was simply an approach to measuring behavior. During its early years, the stakes for psychology were high, consisting of no less than legitimacy in the scientific community.

Both during Richter's time and earlier, several already legitimate systems competed for expression in physiological neurobiology, which was anchored to psychological functions (Broca 1861/1960). These included clinical teachings linked to the study of drives (Freud 1920/1975) and a formidable tradition in the field of psychophysics (Fechner 1860/1966; Helmholtz 1867/1963; Boring 1929/1950; Hilgard 1987). Adolf Meyer, who had been educated in these ideas in Europe, transmitted the rich continental tradition to the young Richter.

Closer to home at Hopkins, and elsewhere, were the great debates between vitalism and tropism (Jennings 1907; Loeb 1918/1973). These debates centered on the question of what were the underlying experimental and conceptual frameworks for behavior and psychology (Pauly 1987). Richter was intrigued by many intellectual disciplines, but he did not belong to any of them in any real sense, at least not at the level of public debate of ideas.

The battle was on for how to make psychology into science. Robert Yerkes (1903, 1913), well known for his comparative work, set out to study the biological basis of behavior and, in particular, comparative intelligence. Yerkes interacted with many competing voices, including Watson's, but Yerkes came out finally for the study of "organic behavior." Psychobiology, for Yerkes, as it would be for Richter, was about biological adaptation (Yerkes 1921, 1930).

PSYCHOBIOLOGY

When Richter set up his laboratory, a few individuals had written on the subject of psychobiology. These included Knight Dunlap, a psychologist at Hopkins. Dunlap's book on psychobiology made some reference to behavior, but very little (Dunlap 1914); further discovery would await Richter (see Dewsbury 1991 for a history of psychobiology). Meyer, like many other investigators of the day, provided his own orientation to the study of psychobiology. The emphasis for Meyer was on "total self-regulatory behavior." This would be a constant experimental theme for Richter. Indeed, Richter went far beyond Meyer, who remained wholly theoretical. In contrast to Meyer, Richter rarely looked up from his data.

There are a number of meanings associated with the term *psychobiology* (Dewsbury 1991). Perhaps the clearest sense is that which posits biological explanations for behavior. Meyer, who wrote extensively on this topic, emphasized long-term adaptation and organismic responses to ecological perturbations (see also Dewey 1925/1989).

PSYCHOBIOLOGY AND CLOCKS

Richter thought cyclic behaviors were internally generated. Two issues stood out for him: regularity and uniformity. These would be themes in all of his work on biological rhythms, as would the idea that pathology revealed important sources of information about the normal function of the clocks.

Clocks keep time and provide the order and coherence required by the outer world to which we try to adapt. Cyclical representations have a long history, which Richter appreciated. Harmonic relationships, as Greek thinkers understood, represent the cycles of events. Many thinkers over the years embraced the cyclic nature of events and their fixed patterns of expression. With the advent of Darwinism, fitness and long-term survival became linked to cyclical events. The study of the clocks that underlie behavior anchored research to real-world events and to a prized human invention, the mechanical objects made for measuring and depicting time.

The biological revolution was at hand: Darwin's revelations about adaptation, speciation, secondary sexual characteristics, and problem solving. The machinery varied in design and niche because nature selected the features of good fit.

Richter embraced two key questions. The first involved the idea of machine design: How would an engineer design a particular behavioral or physiological expression? The second was: What were the causes of spontaneous expression? These themes reflected the horns of the dilemma of determinism versus free expression.

INTERNALLY GENERATED BEHAVIORS: A VIEW OF SPONTANEOUS BEHAVIORS

Bernard noted that "spontaneity enjoyed by beings endowed with life has been one of the objections urged against the use of experimentation in biological studies" (Bernard 1865/1957, p. 5). Richter believed that spontaneous expression was an outgrowth of biological clocks. This would constitute, in part, a solution to the problem of spontaneous behaviors.

In Richter's view, the clocks themselves were fixed. Spontaneous behaviors were a way to conceive of animal behavior that was internally generated and not externally caused. Of course, the clocks reflected the events of nature, the daily and seasonal rhythms. The internal generators were at the heart of spontaneous behavior; they were biologically based. Again, one has to place this in a historical setting, namely, Watson's laboratory (Rozin 1976a). Moreover, the generators were something that an engineer could understand. For example, an engineer could design a piece of machinery to express something every twelve hours on the clock despite rain or snow. Spontaneous behavior reflected internal generators under the mechanism of natural selection, serving a behaviorally and physiologically adaptive set of functions. Thus, biological cycles were internally generated.

In his first major review, "A Behavioristic Study of the Activity of the Rat," Richter laid out his approach to the study of behavior (Richter 1922). But this bore no resemblance to the behaviorism of Watson. Again, what Richter meant by a "behavioristic" study was the measurement of behavior, something objective. Behavior, Richter (echoing Meyer) argued, was about the whole organism adapting to circumstances. "Interest in human psychology is moving rapidly toward problems of general adaptation involving responses of the whole organism in actual working life situations" (Richter 1922, p. 1).

Richter outlined an approach in which the various organ systems of the individual would be studied, not in isolation from one another, but as a "total organism." For purposes of objectivity, he would first derive measures of an animal's activities—eating, drinking, moving, defecating, and other activities—under ordinary conditions, and then look at these behaviors under irregular conditions or perturbations. Richter wanted to understand what he called "the dynamic of behavior" or, quoting Meyer, "experiments of nature"—diseases of normal behavioral expression. After all, Richter worked in a psychiatric clinic where curing behavior was a fundamental end point of inquiry. But Richter's approach was as an engineer in a clinical setting. He was concerned with determining the origins and mechanisms of animal activity.

THE STUDY OF SPONTANEOUS BEHAVIOR

Before Richter there was a paucity of research investigation on animal activity. Richter would create a way to measure behavior and what he called the study of "gross bodily activity" by developing an activity cage and manipulating variables such as light.

Richter monitored the whole activity of the animal with his multiple-cage activity method (fig. 2.1). He suggested that the multiple-cage approach would produce an animal more "intelligent," or more fit, than those raised in less enriched environments (Richter 1922, 1927a). Other researchers would eventually show that enriched environments could foster cortical changes and facilitate a broad array of problem-solving proclivities not seen in rats raised in more impoverished environments (e.g., Rosenzweig and Bennett 1996).

In his thesis Richter developed numerous ways to monitor behavior. For the activity cage, for example, Richter attached to the corner of each cage a

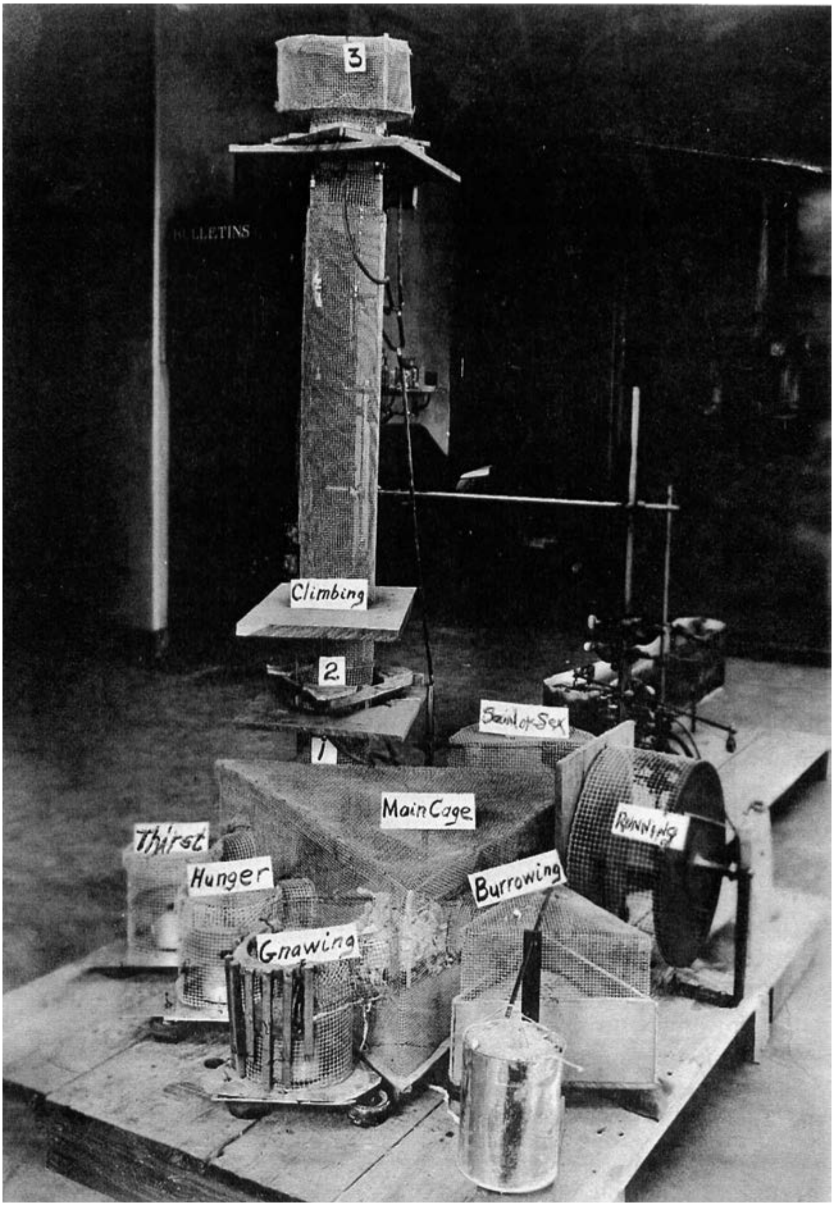

FIG. 2.1. Activity chambers in which various behaviors were monitored, including thirst, hunger, gnawing, running, burrowing, climbing, and mating. *Source:* Richter 1927a

"rubber membrane tightly over a large tambour. The tambours are connected together immediately under the cage into one tube which is led to a small Marey tambour, the lever of which records on the smoked paper of a kymograph." Every movement of an animal, even the slightest, was recorded on the drum with a single mark (Richter 1922, p. 5).

In his experiments, Richter observed alternating patterns of activity and inactivity in rats. He noted that the patterns of active behavior varied between individual rats and with age. In young rats, the rate of alternation between activity and inactivity was much greater than in older animals. Richter noted that this pattern of behavioral alternation was present in the newborn rat and presumably was an innate, hard-wired behavioral pattern expressed in a variety of animal species.

Richter then asked, what happens to the activity patterns when external conditions vary? Say, with hunger? Rats were given a diet adapted from McCollum, a nutritionist at Hopkins. (Many of Richter's diets were derived from the McCollum diets; see chapter 3.) He noted that activity initially increased when the animals were deprived of food but given access to water but began to decline by the fourth day without food. By contrast, rats deprived of both water and food had decreased activity levels very early in the experiments.

Richter showed that rats were inactive after a bout of eating. This phenomenon would later be linked to "postprandial satiety," in which inactivity after a meal is indicative of the mechanisms of digestion and absorption. G. Smith would later comment that one of the figures from Richter's 1922 paper "depicted the critical part of the satiety sequence. . . . When rats stop eating, they engage in a brief period of non-feeding activity before they rest and go to sleep" (G. P. Smith, 1989, p. 1).

Richter's next step in varying environmental factors and meals was to look at how single meals interacted with activity and drinking patterns and how constant light or different temperatures affected the expression of activity or inactivity. Long periods of darkness, high temperatures, and low temperatures influenced activity patterns. He noted the changes in expression of the activity/inactivity distribution.

Richter noted that rats are nocturnal; they were more active when the lights were off than when they were on. Richter also observed that rats became more nocturnal with increasing age. His work demonstrated that hunger, light, and temperature all altered spontaneous behaviors.

Richter and his colleagues at both the Phipps Clinic and Columbia University observed the sleep patterns of human infants and the alternating expression of activity and inactivity (Richter 1922; Wada 1922). They learned that the origins of gross bodily activity or spontaneous activity are independent of external stimuli. For further research, it would be important to find a way to distinguish and measure levels of activity and the cyclicity of activity.

Richter's thesis work was a breakthrough in the laboratory study of behavior. From his monitoring of eating and drinking and other activity patterns, one could gain a real idea of the behavior of the rat and the effects of manipulations such as food deprivation and alteration of light/dark cycles on that behavior. This orientation toward behavioral analysis would set the tone for the rest of his career.

STOMACH CONTRACTIONS AND ACTIVITY: A PERIPHERALIST PERSPECTIVE

Richter investigated different organ systems and, under the influence of Carlson (1916) and Cannon (1915/1929), focused on the contractions of the stomach, which were thought to be linked to food appetite and activity. Richter hypothesized that the endogenous contractions of the stomach might influence gross activity and inactivity. His results suggested that when the stomach was quiescent, activity diminished; the converse held when the stomach contracted intensely. Contractions of the stomach, when isolated, were periodic and therefore contained an autonomous or endogenous function (Carlson 1916). Richter asserted as the principle that dominated his inquiry that "there is a tendency in all living organisms to maintain a metabolic balance or equilibrium" (Richter 1922). Richter understood as homeostatic regulation the activity and inactivity used to maintain internal balance. The stomach, Richter noted, might not be the only peripheral organ linked to activity and inactivity.

Richter mistakenly placed great weight on the contractions of the stomach, and he thought their intensity was linked to degree of hunger (Richter 1922, 1927a; Cannon 1915/1929; Carlson 1916). When food reached the stomach, Richter suggested, contractions decreased, and food activity and food ingestion decreased as well. Richter noted, however, that he was never able in his animal studies simultaneously to monitor activity, feeding, and stomach contractions (Richter 1922). Nonetheless, he held the view that rats' activity and orientation to food sources were related to stomach contractions.

This theme of internal drives and spontaneous behavior continued in Richter's 1927 paper, in which he noted that a two-hour running activity reflected gastric contractions in laboratory animals. A comparative perspective predominated as Richter looked at several species. Richter and his students and colleagues in the early 1920s observed human newborns, rats, and other species to discern the role of the stomach in animal activity, drives, and orientation toward objects. They studied the whole of animal activity. However, not a statistic can be found among their research data, which was not uncommon in Richter's day.

Richter suggested that rats eat, under his laboratory conditions, about seven times a day. Drinking was associated with eating in the laboratory, and Richter found that the rat drank about ten times a day, at intervals of about two and a half hours. Of course, this depended on the water content of the food and the link between drinking and eating (see, e.g., Kissileff and Epstein 1969). Richter again monitored the whole activity, from what went into the animal to what went out of the animal. Richter was beginning to establish an important role of internal oscillators (Richter 1922), that "the regulatory anticipation of the feeding periods may also be explained on the basis of the clock-like functioning of the internal organ" (Blass 1976, p. 43).

A decade later, in an influential article, Karl Lashley noted that the sustained motivation for food of food-deprived animals did not depend on the two-hour rhythmic patterns generated by the stomach (Lashley 1938/1960). Neural programs generated the motivation to search for food (Hebb 1949; Stellar 1954). Moreover, we now know that stomach contractions, and the stomach in general, play a role in food satiety (e.g., Wirth and McHugh 1983) but are neither necessary nor sufficient to initiate hunger (G. P. Smith 1997). Instead, the brain orchestrates the behavior. Richter was still under the spell of the peripheralist physiological perspective (e.g., Cannon 1915/1929) which was part of the zeitgeist.

ORGAN SYSTEMS THAT INFLUENCE ACTIVITY

Richter was one of the founders of behavioral endocrinology. He looked at natural variation in the endocrine cycle as well as the influence of removing endocrine tissue and of injecting hormones to replace a lost endocrine system. His approach, as always, was concrete; in many of these experiments he removed tissue from the gland in question and placed it elsewhere in the body, in some cases injecting it into the corner of the eye (Richter 1956d).

The Gonadal Organs. Richter and his colleagues studied the effects of the ovarian cycle on spontaneous behaviors. They corroborated and extended the finding that the ovarian cycle in the rat operates on a four-day activity rhythm (Wang, Richter, and Guttmacher 1925).

Wang found that running activity was at its highest during sexual receptivity in the female rat and that running, cycling, and receptivity depended on ovarian secretion or function. Removal of the ovaries reduced the running activity and ovarian grafts restored it (Wang, Richter, and Guttmacher 1925).

Richter and Hartman (1934) demonstrated that gonadectomy dramatically decreased running activity and that replacement by gonadal transplant restored activity patterns. Wang, Richter, and Guttmacher (1925) noted an important sex difference: females ran faster and longer than males. They found that running activity was less altered by removal of the testes in males than by removal of the ovaries in females and that implants of ovary extracts in males increased their running activity.

Because Richter's work was housed in a hospital, he had access to patients and medical resources. In an interesting study, he exposed gonadectomized male and female rats, via graduated drinking tubes, to the urine of women who were seven to nine months pregnant. Richter wondered whether the products in the urine would affect running activity. The result: the running activity of ovariectomized females returned to normal, and vaginal smears demonstrated a physiological effect (fig. 2.2). Richter inferred that estrogen and other substances in the urine had effects on both running activity and the reproductive tract (Richter 1934d).

The Pituitary Gland. Hypophysectomy decreased spontaneous running activity in rats (Richter and Eckert 1936). Injections of various pituitary extracts restored the activity. Again, as in all experiments, Richter and his colleagues provided means of animals over days. Changes in end-organ systems were noted; there were decreases in the size of the thyroid, gonadal, adrenal, and pancreatic glands. Replacement therapy, both by injection and by implanting tissue on the corner of the eye, restored to various degrees the behavioral and physiological functions of these end organ systems.

The Adrenal Gland. Adrenalectomy dramatically decreased running activity and adrenal implants restored it (Richter 1936c). Richter surmised that the cortical tissue facilitated recovery, and indeed this is where aldosterone—the salt-retaining hormone—is synthesized. Richter noted that the survival rate

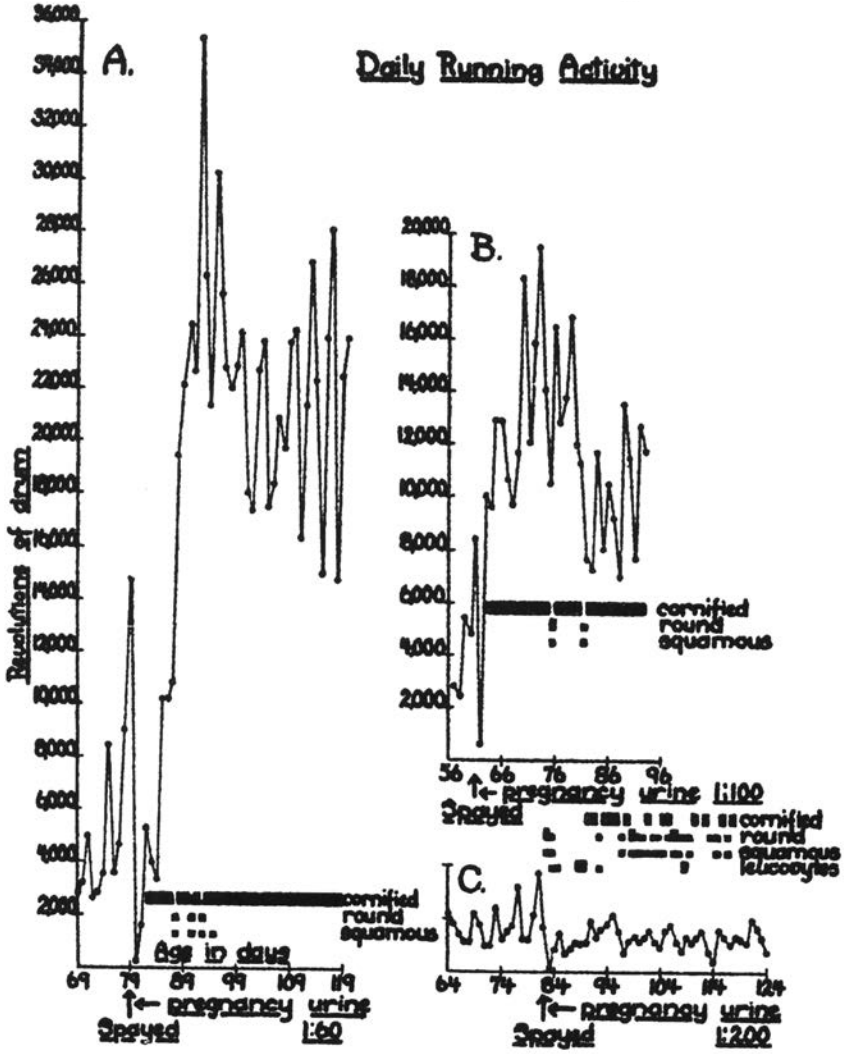

FIG. 2.2. A: The effect of pregnancy urine in 1:60 dilution on the daily running activity of a spayed female rat; also the effect on the reproductive tract manifested in the vaginal smears. B: The effect of pregnancy urine in 1:100 dilution on activity and the reproductive tract. C: The effect of pregnancy urine in 1:200 dilution on activity and the reproductive tract. *Source:* Richter 1934d

after adrenalectomy was less than 50 percent. He inferred that two hormones in the adrenal gland were essential; one kept the animal alive and the other kept it running.

By changing its glandular function and competence through adrenalectomy Richter challenged a rat's internal milieu, its metabolic and nutrient balance (see chapter 3). But in several experiments, he directly manipulated diet to determine the effects on running activity.

The Thyroid and Parathyroid Glands. Thyroidectomy also decreased running activity in rats. Richter had already noted this variation in behavioral activity and the important endocrine characteristic that just a small amount of endocrine tissue was necessary for running activity to be expressed to its full extent. This would become an important theme in the ablation studies and the behavioral performance of many end-organ systems. The replacement of thyroid extracts restored running activity in thyroidectomized rats, and their water and food intake returned to normal (Richter 1933c).

Richter noted that thyroid levels affected biological rhythmic behaviors. The reduction of thyroid hormone levels routinely decreased activity. Moreover, parathyroidectomy, which affected calcium metabolism (see chapter 3), also affected rhythmic behavior (Richter 1933c). Both endocrine systems were subsequently linked to behavioral activation and depressive states in humans (McEachron and Schull 1993). Ablation of the thyroid gland rendered the rat vulnerable to thermal dysregulation, the behavioral adaptation for which was nest building. The behaviors all increased heat production, through running.

BEHAVIORAL REGULATION OF TEMPERATURE

Richter's dissertation included work on the nest-building activities of the rat. He continued this work with Elaine Kinder, who did the research for her Ph.D. in Richter's laboratory and further demonstrated the elaborate nest-building behaviors of the laboratory rat (Kinder 1927), measuring the number of paper strips rats used to build their nests (fig. 2.3).

Once again, Richter argued that the expression of nest building is "practically independent of experience, since young rats 30 days old raised in sawdust build a perfect nest out of the crepe paper the first time it is presented to them" (Richter 1927a, p. 88; Blass 1976). These behavioral responses are instinctual or innate. Richter demonstrated in the laboratory an important

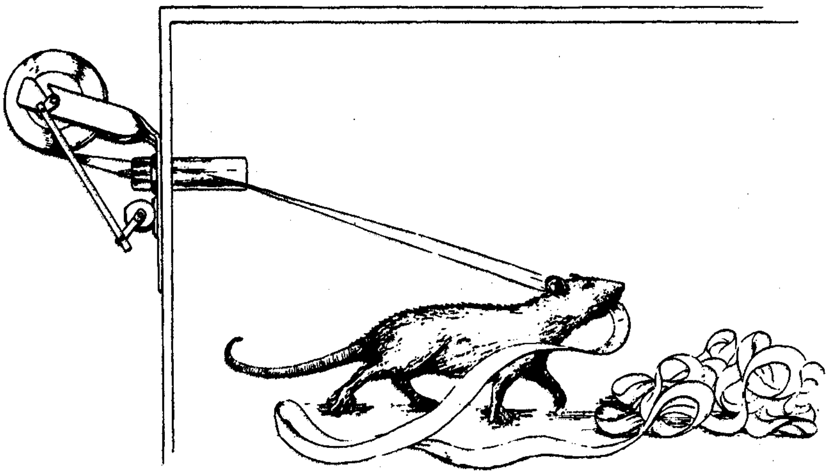

FIG. 2.3. Nest-building behavior. *Source:* Kinder 1927; Richter 1942–43

behavioral adaptation in the regulation of the internal milieu, namely, the behavioral regulation of temperature homeostasis.

THE CIRCADIAN CLOCK

One key feature that facilitates activity and inactivity in some animals is the light/dark cycle. Richter studied the running activity of various species. The difference in running activity of rats with the lights on and off is shown in figure 2.4. A circadian clock is important for the onset of this behavior (Richter 1959b).

Circadian clocks orient and synchronize an animal's adaptive behavioral and physiological responses to periodic changes in the environment. The clock is a fundamental timing device expressed and present in a wide variety of species (Wehr et al. 1993). Richter studied the behavioral whole-organismic expression of circadian rhythmicity, believing in the independence of the clock from external and internal interference. His metaphor for the circadian clock was a wristwatch keeping time. Richter—mistakenly, it would turn out—believed that the circadian pacemaker was "free of all feedback" (Richter 1965; Rusak and Zucker 1979).

Richter provided an inquiry into the phenomenon, not a settled record of the facts. He noted that variation in hormonal levels affected both the estrous

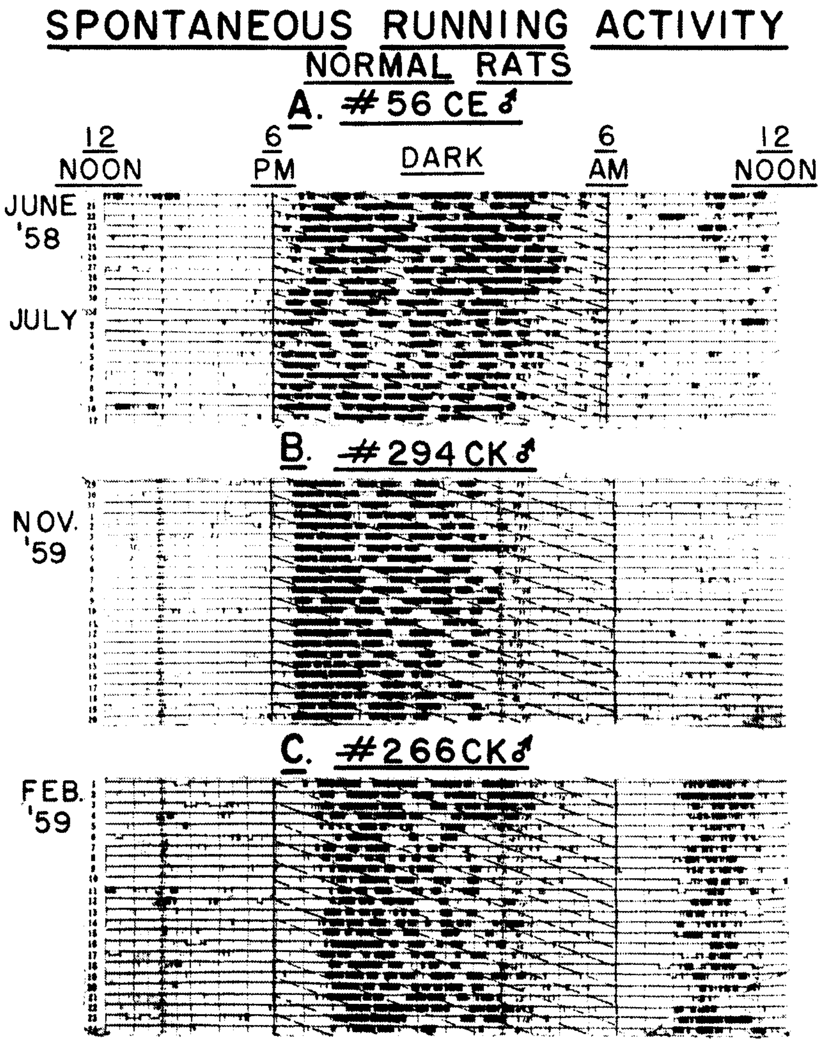

FIG. 2.4. Running activity during the dark and light phases. *Source:* Richter 1965

cycle and running activity in rats but mistakenly assumed that the clock could not be changed by this variation. Hormones can indeed affect the hard-wired expression of the circadian clock and alter the pattern itself; the hands of the clock can be changed somewhat by various hormones, such as estrogen (Morin, Fitzgerald, and Zucker 1977), or by activity or novelty alone (Mrosovsky and Janik 1993). Richter and his colleagues ablated many regions of the nervous system and determined the effects of these ablations on circadian rhythmicity. He approached his subjects from the purview of long-term studies, in some instances studying a subject and behavior over years.

Richter discovered that an ablation "somewhere in the hypothalamus" disrupted circadian rhythmicity. He reported that producing lesions on the hypothalamus resulted in disruption of circadian rhythms. Richter did not often present histology for his brain lesion inferences, but he did show one case in which a tumor disrupted circadian rhythmicity (Richter 1965).

Later it would become known that Richter had indeed been close to localizing the region of the brain essential for circadian rhythmicity when he noted that damage to the hypothalamus disrupted circadian rhythmicity (Richter 1965). In the early 1970s, two groups of investigators concurrently uncovered the essential role of the suprachiasmatic region (SCN) of the hypothalamus, which receives retinal information directly (Moore and Eichler 1972; Stephan and Zucker 1972). Richter himself reported that damage by a knife-cut in this region disrupted the regulation of behavior by the twenty-four-hour clock (Richter 1978a).

Richter was prescient, as were several of his colleagues (Aschoff, Gerecke, and Wever 1967; Aschoff 1981), to believe that the circadian clock was ancient and present in single cells. In fact, we know that many end-organ systems in the body have twenty-four-hour rhythms; for example, the activity of liver enzymes varies with the time of day. Richter was also prescient to suggest the independence of these clocks within several end-organ systems, both inside and outside the central nervous system, although damage to the SCN compromises some of the clocks' rhythmic patterns.

Richter suggested two types of sleep regulatory mechanisms, one linked to homeostatic requirements for sleep and the other to circadian rhythmic activity. He suggested that sleep activity was tied to the reticular formation and perhaps beholden to homeostatic needs (Richter 1967c).

How Many Clocks? Richter surmised that there were multiple clocks. A study of individual animals showed some variation in the clocks under normal conditions; these were further exaggerated under pathological conditions. He noted clocks in the Norway rat with cycles of 1–2 hours, 24 hours, 4–5 days, 12–14 days, 14–22 days, 30 days, 40–60 days, 76–124 days, and 160–180 days, and in other species, some with exceptional duration, like one in the chipmunk with a cycle of 6.5 years (Richter 1965). In fact, Richter's emphasis on individual differences, and perhaps his nonuse of statistical analysis, allowed him to pay more attention to this variation in clocks than many others in the field later would.

Richter noted variations in the adrenal glands of wild rats captured in different seasons. The adrenal glands of rats captured in the summer were smaller than those of rats captured during the early winter. The difference was more striking in males than in females. He claimed that male adrenal glands were 50 percent heavier in rats captured in the early winter than in rats captured in the summer (Rogers and Richter 1948).

Many studies have demonstrated seasonal clocks linked to hibernation and sexual activity. Variations in testosterone and luteinizing hormone concentration are linked to the seasons of spring and summer and to sexual reproduction activities (Nelson 1995). Seasonal physiological and behavioral changes in animals are commonplace and underlie many adaptations.

The Discovery of Fire. Richter had tagged the importance of the twenty-four-hour clock in a variety of species, noting species variation (whether the animals were nocturnal, etc.). The clocks were expressed by neonates and functioned to organize both behavior and physiology (Richter 1977a).

Richter held the view that human beings were less under the influence of circadian rhythmicity than other mammals because of inventions such as the use of fire. In some respects, this point of view reflected a variant of his view of domestication—the effects of cultural evolution on our internal organs.

Experiments in humans by Aschoff, Gerecke, and Wever found that men who remained in soundproof chambers and in constant light still displayed circadian rhythmicity (Aschoff, Gerecke, and Wever 1967). Despite these findings, Richter believed that under normal conditions, not extreme or pathological conditions, the twenty-four-hour clocks lay “submerged” in us, a piece of biological adaptation dormant in physiology and behavior. He certainly was wrong about the internal physiology. Many studies have shown that circadian rhythmicity underlies a variety of physiological functions in normal people. For example, variation in the light/dark cycle results in predictable changes in melatonin, prolactin, and other endocrine measures in many animals, including humans (Wehr et al. 1993). We did not lose this ability because of culture. Of course, cultural effects on biological adaptation were part of the underlying intellectual current for Richter and other investigators, principally Charles Darwin and William James.

With the control of light, our dependence on the internal twenty-four-hour clock became less important and less visible, except under conditions of pathology and emergency. Richter thought this was because of our cultural evolution. He commented that "probably the most important effect produced on early man was the great increases in waking hours" (Richter 1977a, p. 59). Further, he suggested that "these extra hours could be used for cultural and intellectual purposes" (Richter 1977a, p. 59). There was an interest in circadian clocks in Europe, but mostly those in plants and insects (Bunning 1963). Richter had the important insight that the biological clocks evident in plants and insects were also well represented in reptiles, birds, and mammals (Bunning 1963), and he added an interest in the regulation and expression of behavior and physiology. He inferred that great biological variants in adaptations to local niches figure in physiological and behavioral adaptations.

THE SHOCK-PHASE HYPOTHESIS

The shock-phase hypothesis is a biological hypothesis for the emergence of synchronicity as an adaptation. Richter offered this theory to account for the large expression of clocks or cycles. After an insult to the body, a new cyclic phenomenon emerges. Richter thought that bodily pathology reflected aberrations in the timing mechanism of circadian clocks and that, in humans, pathology allowed us to see clocks that were not normally revealed. A shock to the system invokes more synchronicity between organ cyclic phenomena, though it is important to distinguish shock effect from rhythmic patterns.

Do aberrations bring out more oscillatory responses? Yes, but we still don't know how many. Is the shock phase hypothesis warranted? According to Benjamin Rusak, a leading expert in the field, it is.

> Despite the lack of scientific interest in the shock-phase hypothesis for many years, an intriguing recent study lends some general support to the idea. A study of cultured fibroblasts demonstrated the emergence of several circadian cycles of gene expression in response to a single (hence, aperiodic) shock of high concentration serum delivered to the culture system. This observation suggests that even cells that appear to have no inherent rhythmicity may begin to express rhythms in response to a single external perturbation. It is possible that the external stimulus acted to synchronize rhythmic but asynchronous cells or to initiate rhythms in cells with an unexpressed potential for circadian rhythmicity. (Rusak 2000, p. 445)

TABLE 2.1. Conditions That May Bring Out Periodic Phenomena in Humans

Trauma	Debilitation
Vascular damage to brain	Thyroid deficiency
High fever	Cerebral arteriosclerosis
Brain tumor	Syphilis
Various illnesses	Parathyroid deficiency
Brain lesions	Severe stress or shock
Lethargic encephalitis	Food and other allergies

Source: Richter 1965

Richter documented a long list of clinical syndromes that were periodic and linked to bodily pathology. Some of the examples he noted were periodic bleeding, Hodgkin disease, Parkinsonian paresis, peptic ulcer, manic-depressive illness, sleep disturbances, and catatonic schizophrenia. Table 2.1 lists the conditions that may bring out periodic phenomena in humans (Richter 1965).

Richter's eye was on therapeutic goals (the clinical practical implications of basic biological research) as well as on normal functioning. He suggested, for example, links between parathyroid and calcium deficiency and depression and between thyroid deficiency and catatonic schizophrenia (Richter 1965). Richter noted parenthetically that "it must be made clear here that this was not a planned experiment" when he discussed some of his work on the effects of endocrine manipulations on rhythmic activity.

Richter compared the periodic catatonia observed by L. R. Gjessing with the effects of sulfametrazine administration on normal rats (Richter 1959b). The laboratory analogue suggested that thyroid hormone is a factor in the catatonic feature of schizophrenia and, Richter thought, that restoring thyroid balance brings a semblance of stability to the body and is fundamental in the organization of activity. Under different experimental conditions, Richter demonstrated how changes in thyroid function resulted in the expression of different cyclic patterns. Subsequent researchers have linked thyroid activation and the regulation of behavioral systems (McEachron and Schull 1993; Bauer, Heinz, and Whybrow 2002).

Richter had a long correspondence with L. R. Gjessing, whose lectures (Chesney Archives), revealed the influence of Richter's thinking. The periodic nature of illness—the fact that at different times of the day or week or month different physical symptoms become manifest and then recede into the background—was a clinical insight that permeated Richter's thinking about biological clocks (see Richter 1965 for more details about his work on clocks).

CONCLUSION

Richter's discovery that clocks are at the heart of the origins of animal activity and inactivity are quite profound. Richter the naturalist held fast to the real world. Richter the engineer tinkered with how to understand the machinations of the design of an internal system that codes and adapts to the environment.

But Richter the psychobiologist noted that "we have found great individual differences in the levels of activity" of the rat, and he suggested that the same holds for humans. He wrote that the endocrine glands were vital for maintaining "total energy expenditure" (Richter 1932, p. 353). Levels of human activity, he suggested, reflected the expression of a variety of endocrine output from the thyroid, adrenal glands, and gonads.

Cyclic internal machinations and the external environment are coordinated into an expression of adaptation. But because the internal milieu is separate from the external environment, active self-regulation lies at the center of our evolutionary landscape. Richter's ingenuity was to show the fundamental link between cyclic rhythms and their self-generation, the connection of the rhythms to the larger environment, and the origins of self-regulation.

Richter was always interested in biological clocks and thought that his psychobiological laboratory revealed something about the diversity of the clocks, including annual cyclicity or seasonal rhythms (e.g., Prendergast, Nelson, and Zucker 2002). But we did not lose our capacity for biological rhythmicity because we learned how to use fire and invented the light bulb. Our SCN did not atrophy; our pineal gland still secretes melatonin. The sense that our biological proclivities were undermined by our cultural advances, or at least that they could be, and that biological clocks were another instance of loss of biological function with advances in culture, was a misguided belief regarding both culture and biology.

Richter was supported in this research by several individuals, two of whom were particularly important. One, of course, was Meyer, and the other was Walter Cannon. Richter's research on clocks was supported in part by the National Research Council. Cannon was very much involved in monitoring Richter's work, including his observations on humans; in one letter to Cannon (Cannon Archives, Harvard University Press, March 1, 1943), Richter noted sadly that "in our work on the cyclic variation in psychiatric patients we had many disappointments, for during the past two years, possibly due to a very rapid turnover of patients, or just poor luck we have found very few who showed good behavior cycles."

In the same year, in Richter's annual report to the National Research Council (July 1942 to February 1943), he noted a fourteen-year-old patient who "showed very regular 40-day cycles in mood and behavior over a 6-month period." He also noted that there was no indication of any abnormality in the endocrine glands, nor any imbalance of mineral content, except somewhat for phosphorus. Richter, it seems, always had his eye on the patients in the clinic.

Richter made important and lasting contributions to the field of chronobiology, the study of the biological clocks that underlie physiology and behavior, though he may be less known than individuals who defined themselves solely in the context of this field (see Aschoff 1981). Because much of Richter's experimental focus was on blind animals, however, he overlooked the important role of the entrainment of clocks by events in the external world, adaptations, or synchronization to the external world.

How many clocks are there? As I have noted, Richter identified quite a number of them. Of course, the number depends on the animal species in question. The most plausible are the twenty-four-hour and the seasonal clocks, but other clocklike rhythmic patterns do exist and reflect the evolution of an organism and the terrain to which it has adapted.

Richter highlighted three features of clocks: those responsive to homeostatic changes, centrally generated pacemakers, and peripheral clocks. He thought homeostatic clocks were the least accurate, because they were subject to the effects of the environment. Central clocks clicked with precision, keeping perfect time. Peripheral clocks are associated with, for example, periodic swelling of a knee or lymphocyte production from the lymph gland. We now know, as Richter suggested, that both central and peripheral clocks are essential to bodily viability (Rosenwasser and Adler 1986; Rusak 2000).

Richter's love of clocks was lifelong and clinically oriented. The clinical manifestations of joint ailments, immune disorders, gastrointestinal distress, salivary secretions, and skin- and brain-related syndromes were all internally generated, he emphasized. Richter, still at it years later, published a paper in 1971 entitled "Inborn Nature of the Rat's 24-hour Clock," in which he demonstrated that the lack of visual sensibility does not deprive the rat of the inherent circadian rhythmicity (Richter 1971). The clocks are innate.

But Richter also emphasized variation and associated clinical syndromes with individual differences. His laboratory was an extension of the clinical ward. The goal of the laboratory was to simulate clinical syndromes in order to study them in detail. He sought to elucidate what turned activity on and off and then to discern its aberrations during pathological conditions—what Richter called "a biological approach to manic-depressive insanity" and other clinical syndromes (Richter 1930a). Richter noted changes in activity and inactivity that resulted from changes in glandular and neural function, work that had practical implications for the study of the role of clocks in depression and psychosis.

Richter's research into biological clocks was quite important; he was nominated for a Nobel Prize in 1981 for his work on "the biological clock as a timer in biology and behavior." Although he did not receive the prize, he achieved wide recognition for this work, which was only a part of his vast experimental contribution.

In the 1960s, research on the inherent nature of clocks in the regulation of behavior and physiology would explode (e.g., Aschoff and Wever 1965; Aschoff, Gerecke, and Wever 1967; Pittendrigh 1974; Aschoff 1981). Richter worked in isolation from what would eventually expand into a community of inquirers devoted to understanding the role of clocks. Perhaps he would have integrated what would become an important part of the idea of circadian clocks, entrainment to external events, if he had been less isolated from others in the field.

According to Irving Zucker, a noted investigator of biological clocks, "Richter may have been without peers in uncovering various rhythms in several species but the idiographic nature of some of his work, absence of tightly controlled, statistically evaluated experiments, diminished their impact, particularly post-1972, when many people joined an enterprise that Richter almost single-handedly kept alive for several decades. I was certainly stimulated and encouraged by his work" (I. Zucker, pers. comm., 2002).

Richter's obituary, which appeared in the *New York Times* on December 22, 1988, began: "Curt Richter, credited with the discovery of biological clocks, is dead at 94." He began his career with the clocks and thought about them until his death, and was heralded along the way for giving substance to the idea of the biological clock. Indeed, there is no doubt that he did just that. Was he right about everything? No. Was he correct about many features of the big picture? Absolutely!