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# *BIOLOGICAL CLOCKS IN MEDICINE AND PSYCHIATRY: SHOCK-PHASE HYPOTHESIS**,†

By Curt P. Richter

JOHNS HOPKINS MEDICAL SCHOOL, BALTIMORE, MARYLAND

*Communicated September 23, 1960*

Biological clocks in medicine and psychiatry we think of as devices of the body that keep time with relative independence of external conditions and events: each in its own units and with varying degrees of accuracy.

What are these clocks? And where are they located? By all odds the best-known example is the ovarian clock, which for several decades of a woman's life determines the time of ovulation, usually at about 28-day intervals.

What other clocks are there? Why aren't they more readily apparent? What makes them run? What part do they play in our lives? Of what interest are they to medicine in general and psychiatry in particular?

Study of these clocks produces new perspectives on the normal and abnormal functioning of various organs of the body, such as peripheral organs, endocrine glands, and the brain.

It is true that normal human beings give little indication of possessing biological clocks—other than the 24-hour clocks of men and women and the 28-day menstrual clocks of women. But many other timed mechanisms are present, as becomes unmistakably clear under certain abnormal conditions.

These clocks manifest their existence through the appearance of one or more of a number of physical and mental symptoms. Let me give a few examples: first, of clocks manifesting themselves through primarily physical symptoms; and second, of others that become evident through primarily mental or emotional symptoms. (I shall in each case present them in order of the lengths of the units in which the clocks measure time, beginning with the shortest intervals we have detected so far.)

## CLOCKS THAT MANIFEST THEIR PRESENCE THROUGH PRIMARILY PHYSICAL SYMPTOMS

Evidence for the existence of a clock that measures time in the shortest units (12 hours) is presented in the temperature chart of a 19-year-old girl in Figure 1.[1] Ordinates show body temperature readings taken at frequent intervals throughout the day and night. Peaks of 104.2–105.3°F were reached twice every 24 hours. With ascending temperatures the patient was increasingly ill; once the peak had been passed she felt a remarkable relief from symptoms. Blood and other studies failed to explain the fever.

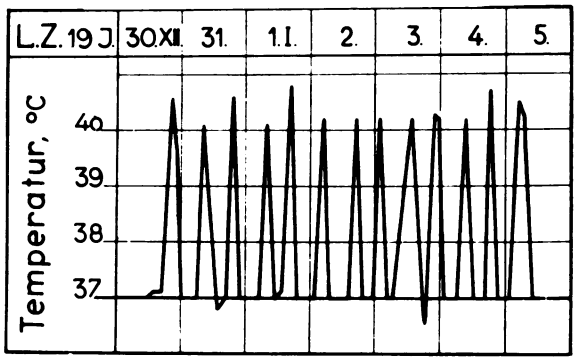


FIG. 1.—Hourly temperature readings showing 12-hour spikes of body temperature in a 19-year-old girl (Hitzig, 1955). These peaks came in a series of 20–28 fairly regular intervals of 5 months. It is noteworthy that these temperature cycles had been present in this patient from early childhood; further that almost identical cycles subsequently appeared in her daughter at the age of 9 months and were still definitely present at the age of 6 years—at the time of the publication of Hitzig's report. During the intervals between each series of temperature peaks, both mother and child were entirely free from all abnormal symptoms.

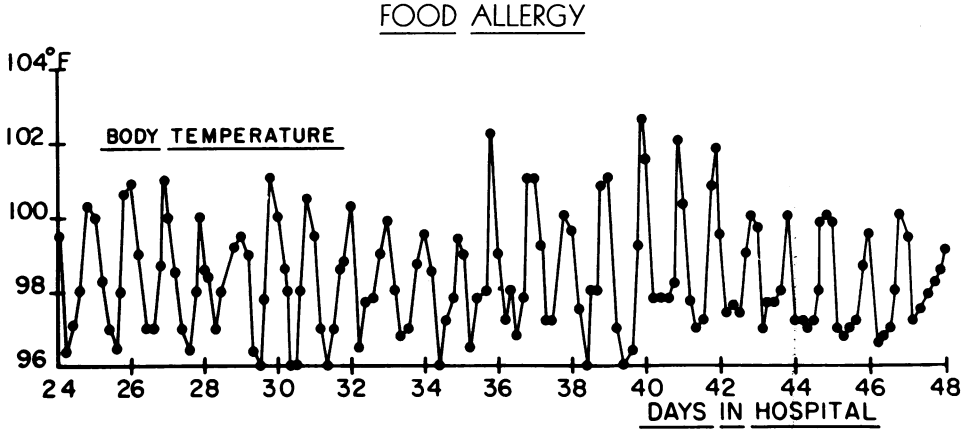


FIG. 2.—Graph showing part of daily records (24–48th day) of 130-day stay in hospital of an 18-year-old girl suffering from food allergy and showing 24-hour cycles. Rowe's cereal-free elimination diet, started on the 122nd day of the patient's stay in the hospital, promptly interrupted the 24-hour fever cycles. (Redrawn from Rowe, 1948.)

The presence of a clock that measured time in units of 24 hours may be seen in the temperature chart of an 18-year-old girl in Figure 2.[2] This patient suffered from a food allergy. Ordinates show body temperature recorded at frequent intervals during the day and night. Body temperature fluctuated at 24-hour intervals not only far above but far below the normal level. During periods of fever the patient experienced cramping in the mid-abdomen and in the rectum; at other times she was free of discomfort.

Evidence for the existence of a clock that measured time in units of 48 hours is presented in the daily records of body temperature and pulse rate of an 8-year-old boy in Figure 3.[1] Since the age of 4 months this boy had shown attacks of fever,

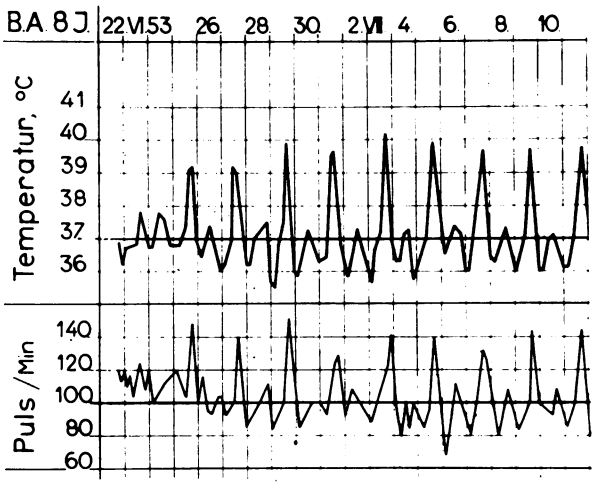


FIG. 3.—Graph showing daily records of body temperature and pulse rate of 8-year-old boy (Hitzig, 1955).

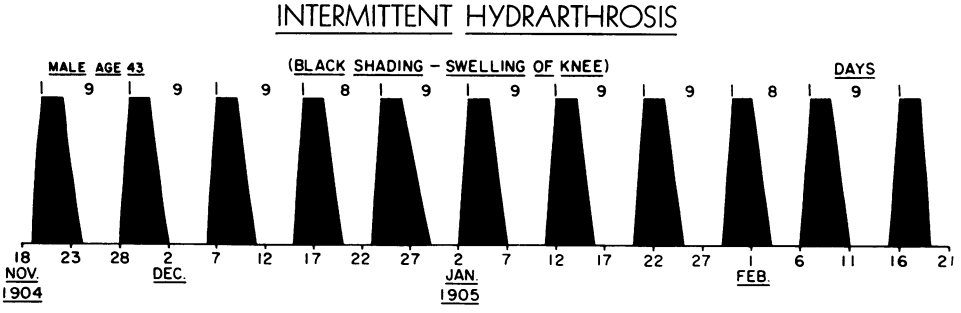


FIG. 4.—Daily records showing periods of swelling of knee in a 43-year-old man with intermittent hydrarthrosis. Lengths of intervals between attacks are shown in days. (This 95-day chart was redrawn from Garrod, 1910.)

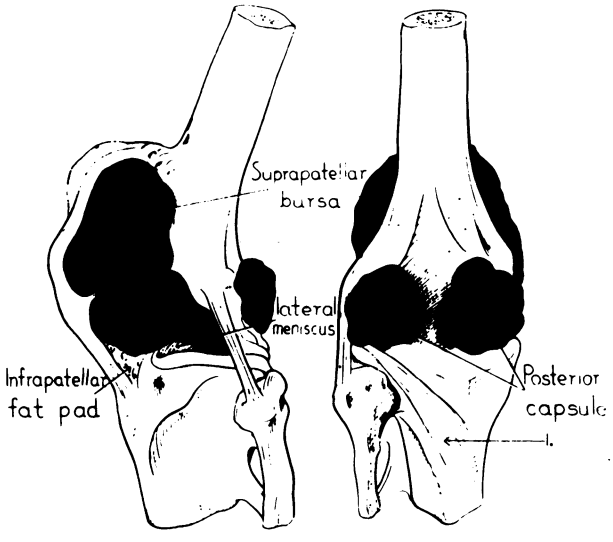


FIG. 5.—Drawings showing the synovial spaces (solid black shading) of the knee. (Modified from Brantigan and Voshell, 1941.)

severe pain in head and chin, polyuria, neutropenia, every 48 hours and lasting 3–5 hours. The original attack occurred after a period of high fever subsequent to small-pox vaccination. Between attacks the patient played and was free of all disturbances. From the presence of an enlargement of the third ventricle, polyuria, and other symptoms, Hitzig concluded that the patient probably suffered from a lesion in the diencephalon.

The existence of a clock that measured time in still longer units (9 days) was manifested in a 43-year-old man by periodic swelling of the right knee (Fig. 4).[3] Solid black areas indicate times during which the right knee was swollen. Intervals between onsets of succeeding attacks are shown in days. In each attack the knee remained swollen 3–5 days; during the remainder of the cycle there was no evidence of abnormality. The synovial spaces that become filled with fluid during episodes of hydrarthrosis are illustrated in the drawing in Figure 5.[4] Many of these patients state that at the start of an attack they have the sensation of water literally rushing into the knees.

Evidence for the existence in one individual of two independent clocks that measured time in units of 7 or nearly 7 days is shown in the record of a 47-year-old man also with intermittent hydrarthrosis (Fig. 6).[5] In this case the chart gives

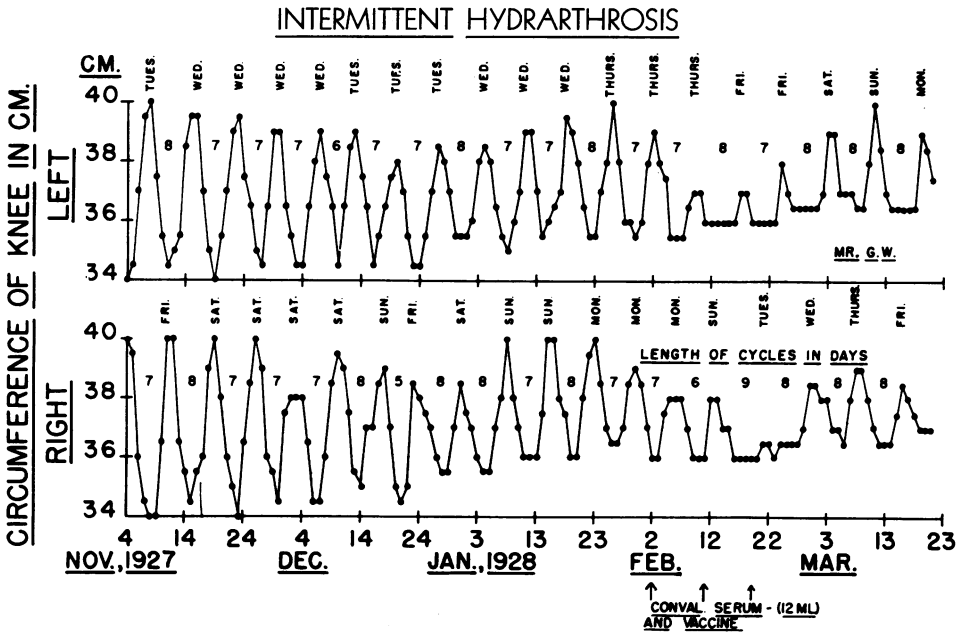


FIG. 6.—Daily records of circumferences of the right and left knees of a patient with intermittent hydrarthrosis. Ordinates give circumference of each knee in centimeters. (Redrawn from Baker, 1929.)

daily measurements of the circumference of each knee in centimeters for a period of 140 days. In many instances the swelling in one knee was at a maximum while it was at a minimum in the other. Thus, at the start of the record, maximum peaks came on Tuesdays and Wednesdays in the left knee and on Fridays and Saturdays in the right.

The presence of a clock that measured time in still longer units (17–19 days) was manifest in the blood count of a 41-year-old woman suffering from cyclic agranulocytosis as seen in Figure 7.[6] The number of polymorphonuclear cells fluctuated between 4,000 and zero every 17–19 days. Lip and cheek ulcers appeared during each cycle just before the number of neutrophils, important defenders of the body against infection, reached these zero levels. The patient experienced malaise coincident with the agranulocytosis. There is evidence here also of the existence of a second clock, the menstrual clock, in this case measuring time in units of 34 days and entirely independently of the other.

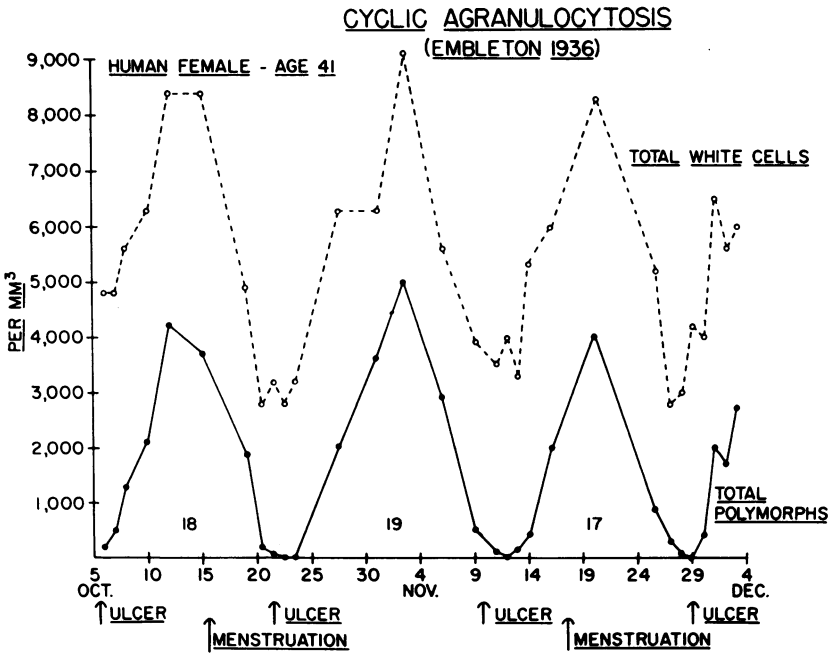


FIG. 7.—Graph showing daily records of total white cells and polymorphonuclear cells per cubic mm of blood in a 41-year-old woman with cyclic agranulocytosis. The lengths of the cycles are indicated in days. Arrows indicate appearance of mouth ulcers and of menstrual periods. (Redrawn from Embleton, 1936.)

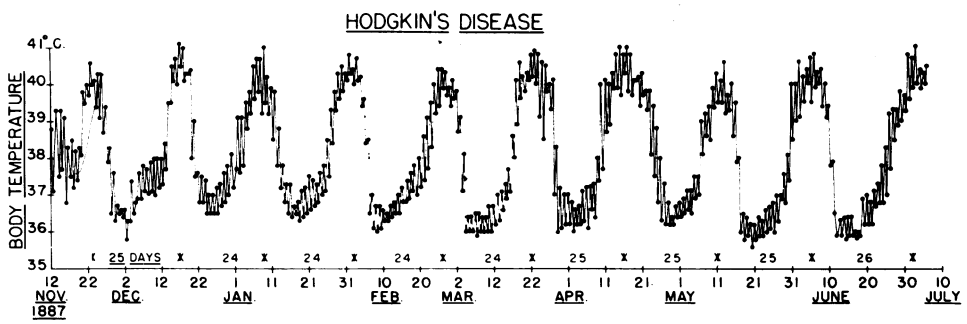


FIG. 8.—Graph showing daily body temperature records of a 19-year-old boy with Hodgkin's disease. The numbers over the base line give the lengths of the temperature cycles in days. (Redrawn from Ebstein, 1887.)

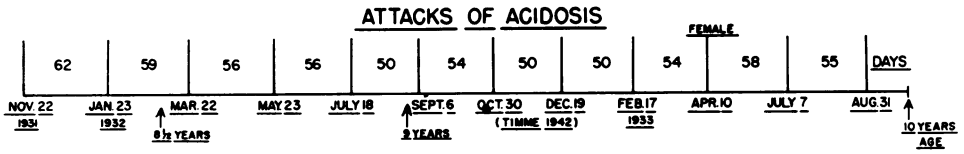


FIG. 9.—Graph showing record of attacks of acidosis in a young girl and length of intervals between attacks. (Chart made from data taken from paper by Timme, 1942.)

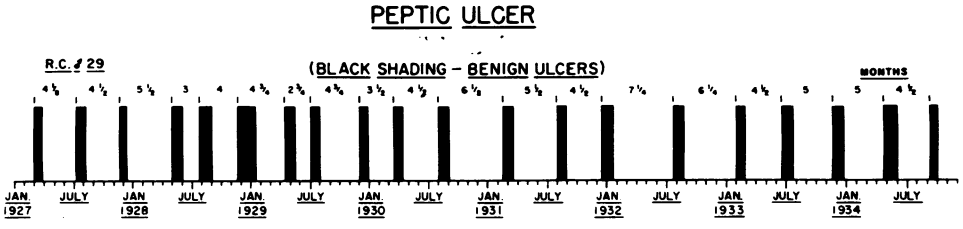


FIG. 10.—Graph for 29-year-old man showing record of appearance of recurrent duodenal ulcers. Solid black shading indicates appearance and duration of ulcers. Numbers at the top show intervals in months between onset of successive attacks. (Redrawn from Jahiel, 1953.)

Evidence for the existence of a clock that measured time in still longer units (24, or nearly 24, days) is shown in the temperature chart of a 19-year-old boy with Hodgkin's disease (Fig. 8).[7] This chart gives daily morning-evening temperatures over a 240-day period. During the periods of elevated temperatures the patient complained of tiredness, headache, loss of appetite, and abdominal pain and showed increased pulse and respiratory rates, loss of weight, splenomegaly, and lymphadenopathy.

The existence of a clock that measured time in units of 52 or nearly 52 days is demonstrated in the chart in Figure 9 which shows the occurrence of attacks of acidosis in a young girl, aged $8^1/_2$ years at the time of the first attack.[8] Beginning at an age of $1^1/_2$ years this child showed definite symptoms of pituitary, thymic, and calcium disturbances, growth abnormalities, and attacks of allergy consisting of skin eruption, asthma, gastrointestinal upsets, and fever. Later, acidosis became the chief symptom of the attacks which persisted up to her 13th year. Treatment with pituitary substance, thyroid powder, and calcium lactate, helped to reduce the number and severity of attacks. Two other of Timme's patients also had attacks of 50–60 days in length.

The presence of a clock that measured time in still longer units ($4^1/_2$ months on the average) is demonstrated in the chart in Figure 10 which shows the occurrence and duration of attacks of benign duodenal ulcers over an 8-year period in a man who was 29 years old at the onset of the illness.[9] During these attacks, each lasting 10–15 days, the patient suffered from postprandial pain.

## CLOCKS THAT MANIFEST THEIR PRESENCE THROUGH PRIMARILY MENTAL AND EMOTIONAL SYMPTOMS

Now let us turn to examples of clocks that manifest their presence through primarily mental and emotional symptoms. Evidence for the presence of a clock that measured time in units of 24 hours was seen in a 28-year-old woman suffering from Parkinsonism subsequent to an attack of encephalitis early in childhood.[10] During

each day up to nine o'clock in the evening the patient was bed-ridden, unable to walk, or to feed herself because of a marked rigidity and tremors of her legs and arms. Her handwriting was indecipherable, her speech unclear; but she was euphoric. Quite sharply near nine o'clock in the evening she showed a sudden change in her whole personality. Rigidity and tremors disappeared; she was able to walk, feed, and otherwise take care of herself; her speech and handwriting became perfectly clear; the euphoria disappeared to leave in its place a state of apathy. Figure 11

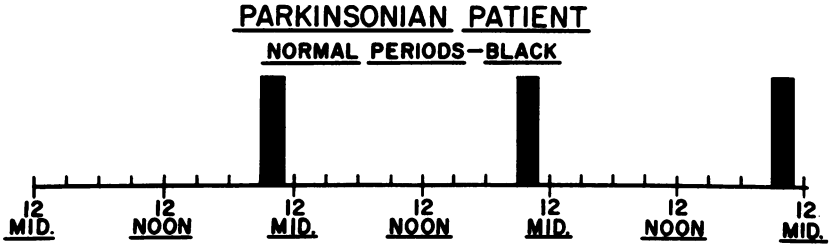


FIG. 11.—Graph made from the clinical report (Leonard, 1931) of a 25-year-old woman with Parkinsonism. The black shaded areas lasting 2–3 hours each 24 hours are periods during which the patient was able to walk, feed herself, talk and write clearly, but was apathetic.

shows a graph of these changes. These 24-hour cycles were present during the nine-year observation period in the hospital.

The presence of a clock that measured time in units of 48 hours is evidenced in the excerpts of a so-called behavior chart (Fig. 12) kept by trained nurses for a

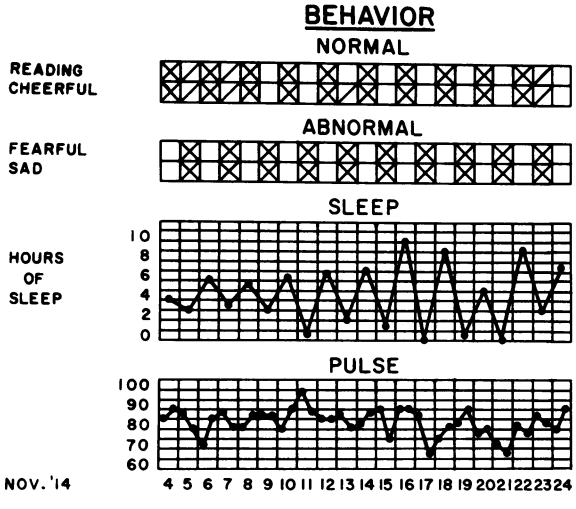


FIG. 12.—Part of behavior chart of 64-year-old woman showing presence or absence of normal and abnormal behavior and mood; also body temperature and pulse rate. A 48-hour cycle is clearly shown in behavior and mood, hours of sleep, and pulse rate. (Richter, 1938.)

64-year-old woman from the Phipps Clinic.[11] The two top rows of squares are marked for normal behavior and mood: reading, cheerful; the two squares in the second row are marked for abnormal behavior: fearful, sad (actually suicidal). Here we see a 48-hour cycle, 24 hours of normal and 24 hours of abnormal behavior. This same cycle is clearly reflected in hours of sleep and definitely, but less clearly, in pulse rate. In this case transition from one phase to the other was very sharp—

often occurring within a few minutes—and at almost exactly the same time on successive nights. This is the same cycle seen in the patient with primarily physical symptoms whose record is shown in Figure 3.

Evidence for the existence of a clock that measured time in slightly longer units (5 days) comes from another Phipps Clinic patient, a 30-year-old woman diagnosed as "constitutional inferiority with hypomaniac features."[12] In Figure 13, which

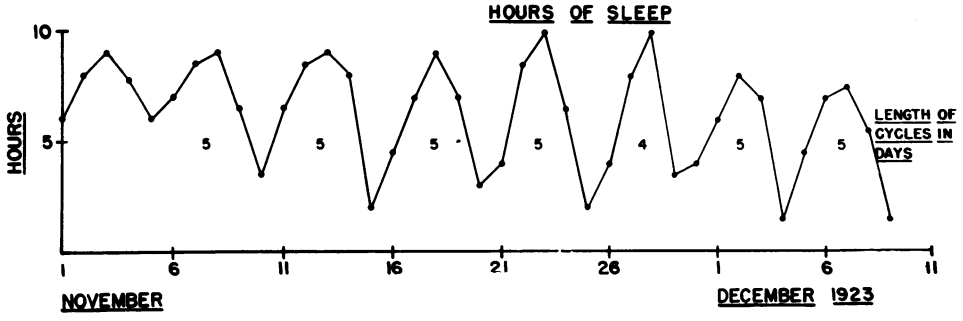


FIG. 13.—Graph showing daily record of hours of sleep of a 30-year-old woman diagnosed as "constitutional inferior with hypomanic features." (Richter, 1934.)

shows hours of sleep, we see the presence of a clock that measured time in units of 5 days. One to two days of excitement and sleepless nights were followed by periods of 2–3 days of sluggish behavior and nights of normal sleep.

The presence of a clock that measured time in still longer units (19–24 days) is evidenced in the daily records of a 22-year-old male catatonic-schizophrenic patient with recurrent periods of excitement (Fig. 14).[13] The top graph repre-

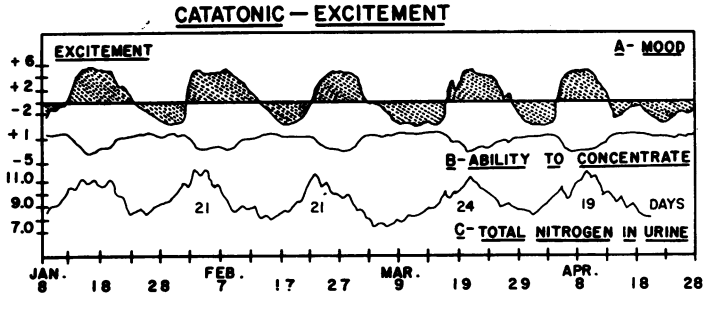


FIG. 14.—Graph showing daily records for 22-year-old male catatonic-schizophrenic patient with periodic excitement. (Redrawn from Gjessing, 1936.)

sents estimates of mood; the second, a measure of the patient's ability to concentrate; the third, total urinary nitrogen. The record extends over a 110-day period. Throughout the entire time, the patient was kept in bed and on a constant diet. This patient was alternately wild and excited, so much so that he had to be forcibly restrained, and then normal or slightly depressed. Here again the transition between the two phases occurred within a very short period. During the excited phases the patient had difficulty in concentration. Sinusoidal cycles of the same lengths appeared in total nitrogen metabolism.

Evidence for the existence of a clock that measured time in units of 40 days may be seen in the excerpt from the daily behavior chart for a Phipps Clinic patient,

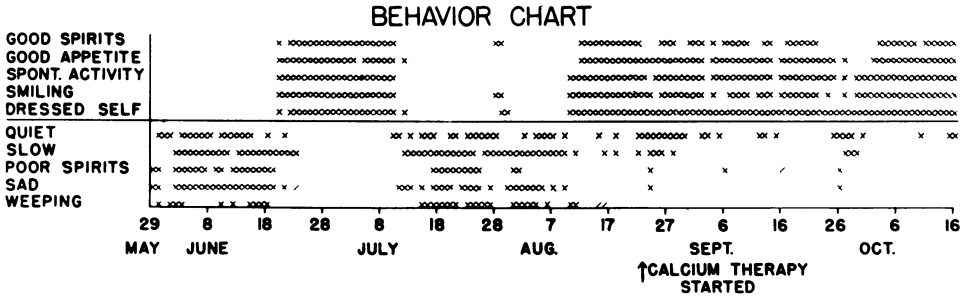


FIG. 15.—Graph showing part of daily behavior chart of 56-year-old woman with apparent parathyroid deficiency. (Redrawn from Richter, Honeyman and Hunter, 1940.)

a 56-year-old schoolteacher (Fig. 15).[14] Markings for normal behavior and mood are indicated above the center dividing line; markings for depressed behavior and mood, below the line. The depressed and normal phases both lasted about 20 days. The change from one phase to another was quite sharp. This patient suffered from an apparent parathyroid deficiency. Treatment with calcium lactate solution and $AT_{10}$ (Dihydrotachysterol) corrected the calcium deficiency and abolished the attacks.

The existence of a clock that measured time in units of 52, or nearly 52, days is demonstrated in the excerpt of the daily behavior chart of a 14-year-old boy (Fig. 16).[15] Markings for manic behavior and mood are shown on the top third of the

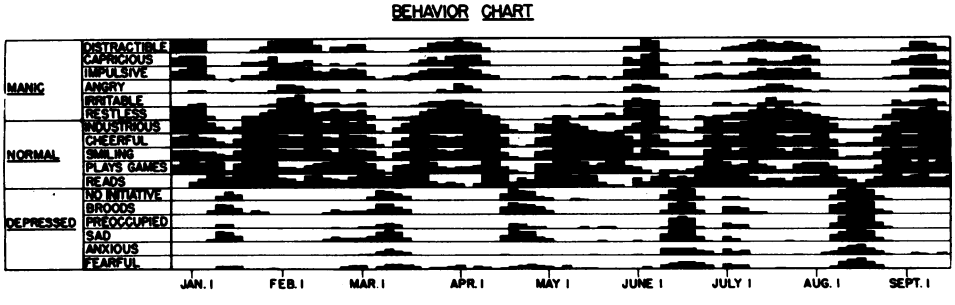


FIG. 16.—Part of behavior chart showing daily record of behavior and mood of 14-year-old boy. (Redrawn from Rice, 1944.)

chart; for normal behavior and mood, on the middle third; and for depressed behavior and mood, on the bottom third. At the age of 14 years this boy suddenly began showing circular attacks that followed a succession of changes in behavior and mood from manic to normal, to depressed, to normal, to manic, etc. He was observed in the Phipps Clinic for $8\frac{1}{2}$ months and in another hospital for 9 months, at the end of which time the attacks still occurred with the same regularity. It will be noted that in this patient with primarily mental and emotional disturbances, the lengths of the cycles were exactly the same as those of the three patients with primarily physical attacks described by Timme.[8]

The presence of a clock that measured time in much longer units, 15–17 months, was seen in a manic-depressive patient during 6 years of her life spent in the Municipal Hospital in Vienna (Fig. 17).[16] The ordinates give weight in kilograms,

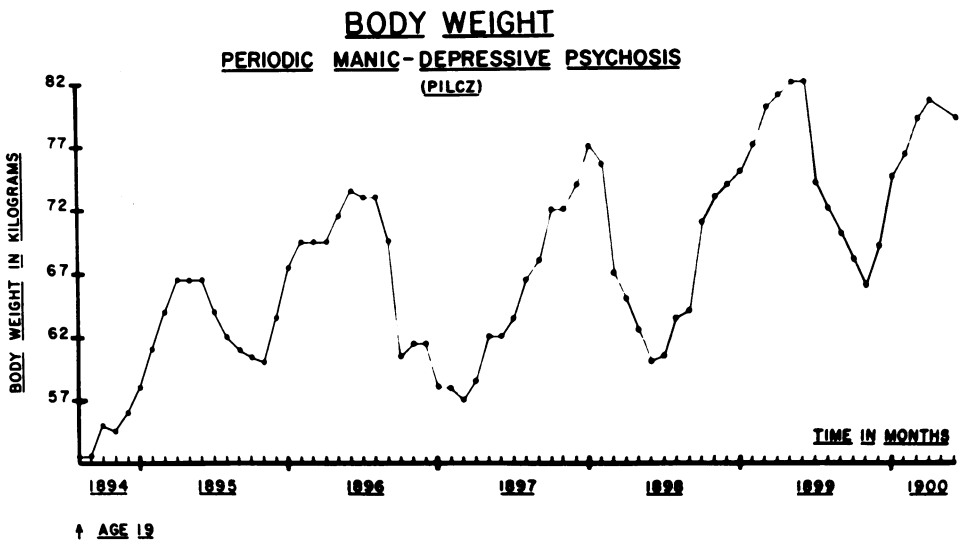


FIG. 17.—Graph showing body weight at monthly intervals of a manic-depressive patient in the Municipal Hospital of Vienna. (Redrawn from Pilcz, 1901.)

abscissas time in months. During manic periods the patient lost weight, which she more than regained in each successive period of normal or depressed behavior.

## CHARACTERISTICS OF BIOLOGICAL CLOCKS

Over the course of years I have collected records of more than 500 patients whose symptoms have occurred with clock-like regularity. Some of the records came from the medical and psychiatric departments of the Johns Hopkins Hospital, some from other hospitals, but most of them came from the literature. I have combed the world literature of medical and psychiatric publications from the XVIIth Century to the present time for reports of cyclic clinical phenomena, particularly for charts showing actual daily measurements. This is the first time all this material has been correlated from the point of view of a biologist rather than that of a clinician, and with special emphasis on the cycles themselves, their duration, and other characteristics. Most records were obtained during the past century and the early part of the present century, when medical men, including psychiatrists, were concerned with obtaining careful detailed records of the clinical course of illnesses rather than with effects of various forms of treatment.

From the standpoint of research it is to be regretted that our increased knowledge and greatly improved means of treatment have led to the elimination of much of the characteristically detailed early reports. Some of the most significant recent records on psychiatric patients were made by a biochemically-minded psychiatrist, Gjessing in Norway, and by his followers in Germany, the United States, and New Zealand. Gjessing kept his patients under strictly controlled situations and kept daily records of many different metabolic and mental functions over long periods of time. Many good records of patients with primarily physical records were made or collected by Reimann.[17]

That we deal here with true "internal" clocks is shown by the fact that the various

physical and mental manifestations recurred with great regularity, in most instances over long periods of time despite marked changes in external conditions to which the patients must have been exposed—such as temperature, humidity, barometric pressure, and other external influences—and despite reactions to the many day-to-day emotionally charged events and occurrences. The attacks occurred with such great regularity that in many instances the person was able to predict months ahead the exact day of an attack—in some instances, not only the day but the hour and even the minute. One man, an insurance company officer, who had alternate days of depressed and normal behavior, showed me his appointment book with alternate days crossed off his calendar many months ahead. Under controlled conditions of a clinic this man had shown 48-hour cycles of metabolic function as well as of behavior and mood. At Cambridge University the schedule for soccer games over a season was specifically arranged so that no game fell on days when their best player. who suffered from hydrarthrosis of an injured knee every 9 days, would be incapacitated.

These various clocks measure time in different units ranging from 12 hours to several years. In many instances each unit consists of two phases; either the one is abnormal and the other normal, or they may both be abnormal. Either may be longer; the transition from one phase to the other is often strikingly abrupt. The relative lengths of the two phases, as well as the nature of the transition from one to the other, may vary from person to person. In some instances the cyclical curve may be sinusoidal. In any one patient the length and characteristics of the cycles tend to remain exactly the same.

These biological clocks may manifest themselves with equal frequency in males and in females and they may appear at any age from shortly after birth to old age. They may persist for months, years, or a lifetime, or they may be evident for only short periods, either to disappear forever, or to return again later.

Further, these biological clocks may manifest themselves with equal frequency in patients whose symptoms are primarily physical and those with primarily mental or affective symptoms—and the units in which their clocks measure time have much the same range, 12 hours to a year or more. Not only do the units have much the same ranges but in a number of instances so far they have been found to have the same lengths. This is most notably true of patients with 48-hour clocks; two such records were presented at the beginning: one showing primarily physical symptoms (Fig. 3), the other primarily mental symptoms (Fig. 12). Instances were also presented in which clocks that measured time in units of approximately 52 days were present in both groups of patients (Figs. 9 and 16 respectively). A number of other such instances are at hand. The further analysis of our data will undoubtedly bring out still others.

In every instance in which examinations of physical functions were made in patients with primarily mental and emotional symptoms, definite evidences were also found for the presence of physical symptoms. This indicates that in the one group clocks manifest their presence by physical signs; in the other, through both physical and mental signs and symptoms.

It may be noted that many psychiatrists have long denied the existence of inherent clock mechanisms in their patients in the belief that recurrences of abnormal mental and affective states result from reactions to recurring emotional stimuli and

disturbing life situations. The close similarity between the clocks of the two types of patients—established here for the first time—indicates that both kinds depend on the operation of inherent cyclic mechanisms.

It is significant that with few exceptions the clocks may manifest themselves through various forms of periodic pathological changes without leaving any detectable lasting physical or mental effects even after years or an entire lifetime of recurrences. In other words, between attacks the individual remains normal, thus providing his own normal baseline for comparison of changes that occur during attacks.

It must be mentioned here that thorough examinations made in many of the patients have failed to reveal the presence of any infectious organisms, the cyclic multiplication of which could account for the periodic changes. It is true that infectious diseases have been found in some of these patients with periodic illnesses, but elimination of the infection did not interfere with the cycles.

It may be mentioned at this point that the results of studies on the experimental production of abnormal cycles of behavior and metabolism in animals carried on since 1921 have helped to provide a more general perspective on the biology of clock phenomena. Results of these studies were summarized in my Salmon Lectures and will be referred to here only in passing.

## NONSPECIFIC SYMPTOMS OF PRESENCE OF CLOCKS

The presence of clocks may be manifested by cyclic changes in almost any organ of the body, as may be seen in Table 1 which lists the organs that in one patient or another have been reported to show cyclic changes—joints, bone marrow, lymph glands, stomach and duodenum, etc., and the respective clinical manifestations; or by cyclic changes in almost every mental or emotional function—stupor, depression, elation, excitement, etc., as may be seen in Table 2, which lists the various symptoms that have been reported to occur in one or the other of patients with periodic psychiatric illnesses.

TABLE 1

ORGANS AFFECTED IN PERIODIC ILLNESSES, AND ASSOCIATED CLINICAL MANIFESTATIONS

| Organs | Clinical manifestations |
|---|---|
| Joints (synovial spaces) | Intermittent hydrarthrosis, pain |
| Bone marrow | Cyclic neutropenia, agranulocytosis (ulcers) thrombocytopenia (bleeding, reticulocytopenia, anemia) |
| Lymph glands | Cyclic lymphocytosis, monocytosis, fever, Hodgkin's |
| Stomach and duodenum | Cyclic peptic ulcers, vomiting, diarrhea, fever |
| Peritoneum | Benign paroxysmal peritonitis, pain, fever |
| Salivary glands | Cyclic excessive secretion |
| Sweat glands | Cyclic excessive sweating |
| Spleen | Cyclic neutropenia, fever |
| Kidney | Cyclic hematuria, oliguria, polyuria, fever |
| Muscles | Familial periodic paralysis |
| Eyes | Cyclic iritis, polyserositis |
| Skin | Cyclic purpura, urticaria, angio-neurotic edema, erythema, fever |
| Brain | Cyclic epilepsy, hypo- and hyperthermia, insomnia, hypersomnia, headache, migraine |

It must now be pointed out that some of these symptoms may be specific for a certain clock unit or for a definite disease, others may not be. The outstanding example of nonspecific physical manifestations is fever. Thus the chart in Figure 18 shows that fever may be an indicator of the presence of any one of the clocks that

TABLE 2

MENTAL AND EMOTIONAL STATES IN PERIODIC ILLNESSES

| | |
|---|---|
| Stupor | Hallucination |
| Depression | Hypo-or hypersomnia |
| Elation | Bulimia |
| Excitement | Dipsomania |
| Mania | Actual changes of personality |
| Paranoia | Hypochondriasis |

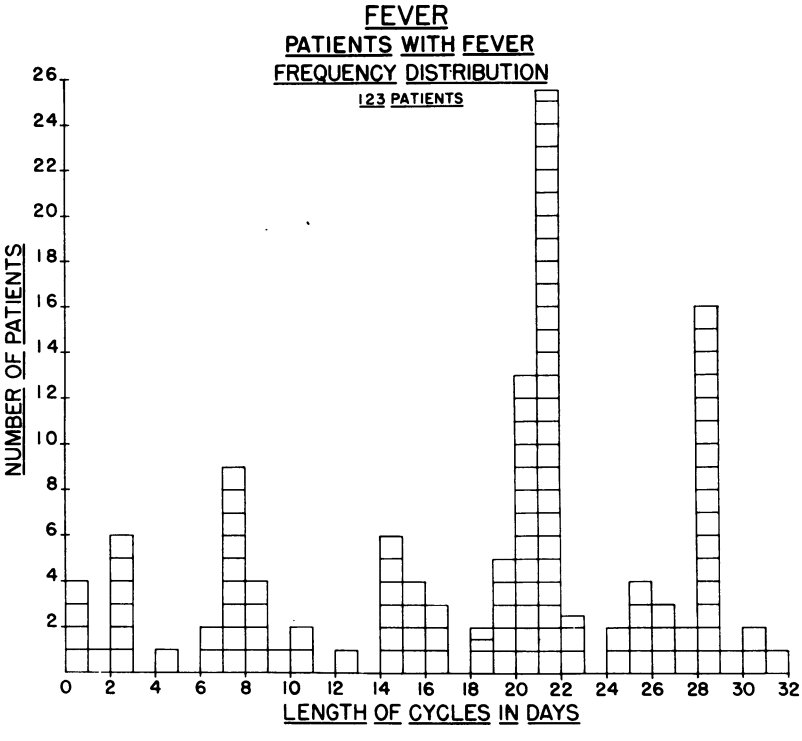


FIG. 18.—Distribution chart from 123 patients in which fever was one of the outstanding symptoms. Abscissas show length of fever cycles in days; ordinates number of patients with each length of cycle.

measure time in units ranging from 12 hours to 30 days, or more. This chart shows the average length of cycle for each of the 123 individuals in whom the presence of a clock was manifested by periodic peaks of body temperature. Abscissas give the length of the units in days; ordinates show the number of individuals having each length of cycle.

It is noteworthy that the fever chart shows maxima of numbers of individuals at 7 days and multiples of 7, namely 14, 21, and 28 days. The possible significance of this remarkable pattern will be discussed at another time.

Data for pulse rate and number of leucocytes are not available for the same large number of individuals but, since in all instances in which data are available, an increased pulse rate and leucocytosis so closely followed fever, it is likely that these two functions follow the same pattern as in Figure 18.

It is possible that most mental and affective symptoms may be nonspecific:

thus stupor may be a symptom of a 48-hour or of a 43-day clock; depression maybe a symptom of a 48-hour, or of a 15-month clock, etc.

How the mental symptoms come to be nonspecific can be learned from histories of patients with a 48-hour clock, 24 hours each of a "good" and "bad" day. These histories show that a fairly close relationship exists between behavior and mental status on "good" and "bad" days and the more or less chronic behavior and mental conditions present before the superimposition of the 48-hour cycle. Thus, in a normal person the presence of the 48-hour clock may manifest itself only through physical symptoms, cycles of body temperature, pulse rate, edema, etc., whereas a schizophrenic may show marked schizophrenic reactions on the "bad" day, reduced or no schizophrenic symptoms on the "good" days, and a depressive patient may be deeply depressed on his "bad" day, cheerful, communicative, etc. on the "good" day.

Of special interest here is the fact that in patients suffering from a fairly constant state of psychotic or neurotic symptoms, the appearance of the clock suffices not only to break up the mental and affective states into 48-hour periods, but to return the patient to a normal or nearly normal condition in the 24-hour period of the cycle.

A full knowledge of the mechanisms of the 48-hour clock—how the clock works—would throw light on the control of the great variety of psychotic and other states which it is able to modify in such remarkable fashion.

We may conceive that fever, leucocytosis, and other nonspecific symptoms have the same relation to the internal clocks that the hands have for an ordinary clock—they are simply indicators of the clock's running.

### SPECIFIC SYMPTOMS OF THE PRESENCE OF CLOCKS AND POSSIBLE SITES OF CLOCK MECHANISMS

Now let us turn to instances in which a symptom or illness is associated with a definitely limited range of clock units, instances in which the symptoms may be a part of the clock mechanism itself. I shall start with intermittent hydrarthrosis, a condition in which we have records for the largest number of patients and also an illness which, as will be seen, offers almost ideal experimental conditions for our purposes: there is no fever, no leucocytosis, no changes in pulse rate, no mental or emotional symptoms—in most instances swelling of the joints constitutes the sole abnormal symptom. In any one patient the lengths of the cycles of swelling of a joint tend to remain so constant over periods of months or years that we are able to speak of a characteristic rather than an average length of cycle. Figure 19 presents the distribution curve of the characteristic lengths of cycles for 128 patients with intermittent hydrarthrosis—all of the patients for whom we have definite records of lengths of cycles. The ordinates record the number of patients showing characteristic cycles of each duration as measured in days. As can be seen, the lengths of these cycles almost all fall within a very narrow range, 7–14 days inclusive. Thus, in keeping with our thinking in the cases already discussed, we assume that these patients harbour clocks that keep time in units coming within this range.

The striking facts concerning the periodicity in this particular syndrome are that although in most patients with multiple joint involvement, swelling occurs at the same time in all joints—that is, all joints have the same lengths of cycles and

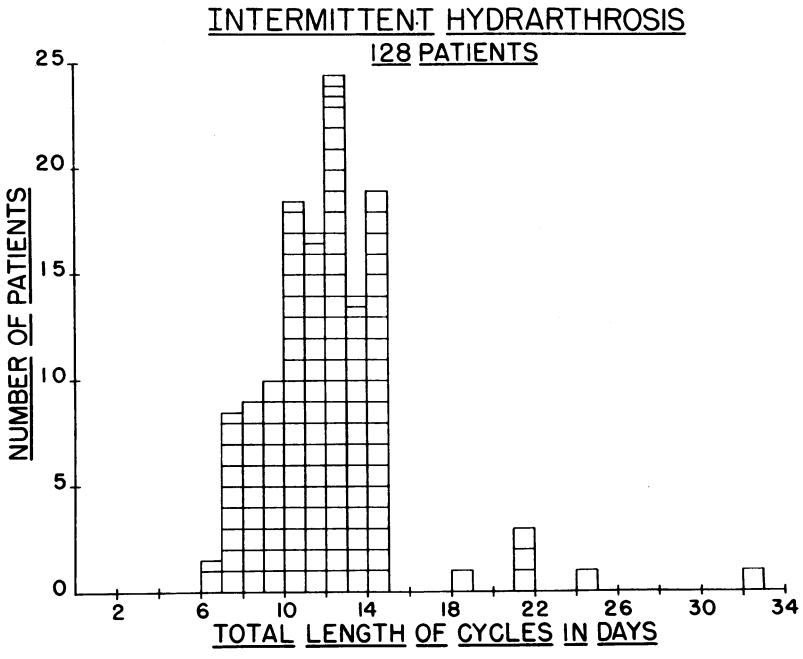


FIG. 19.—Distribution chart for 128 patients with intermittent hydrarthrosis. Abscissas give lengths of cycles in days; ordinates, number of patients with each length of cycle. In most instances the lengths of cycles for any one patient remained the same over long periods of time with only an occasional variation of a day or two.

all are in phase, in some patients, as we have seen, the lengths of cycles may be the same in two or more joints, but the swelling may reach maxima at different times in the respective joints. That is, although the cycles have the same lengths, they are out of phase. In still other patients with multiple joint involvement, the cycles of swelling in three or more joints may not only be out of phase but have different lengths; that is, in one joint it may be 8 days, in another 9 days, in another 10 days. This means that the joints may function quite independently of one another —still, however, within the range of 7–14 days. These observations make it unmistakably clear that the joints function not only independently of one another but of any central control, since it is difficult to imagine influences of these different rates arriving from the brain. Here the clock mechanism must be located in the periphery, presumably in the cells of the joints that secrete synovial fluid.

In similar manner, the distribution curve of the duration of the cycles in 38 patients with cyclic agranulocytosis (Fig. 20, top) shows an even much narrower range at 21 days. The conclusion seems to be inescapable that some mechanism or mechanisms must function in the body with this frequency. Since the chief change observed in these patients is in the number of circulating polymorphonuclear cells, we may presume that this clock is located in the tissue producing these cells. Until now, their life span has only been estimated on the basis of indirect measurements. These estimates fall as high as 13 days.[18]

The distribution curve for the cycle duration of 20 patients with Hodgkin's disease (Fig. 20, bottom) shows a wider but still definitely limited range with a

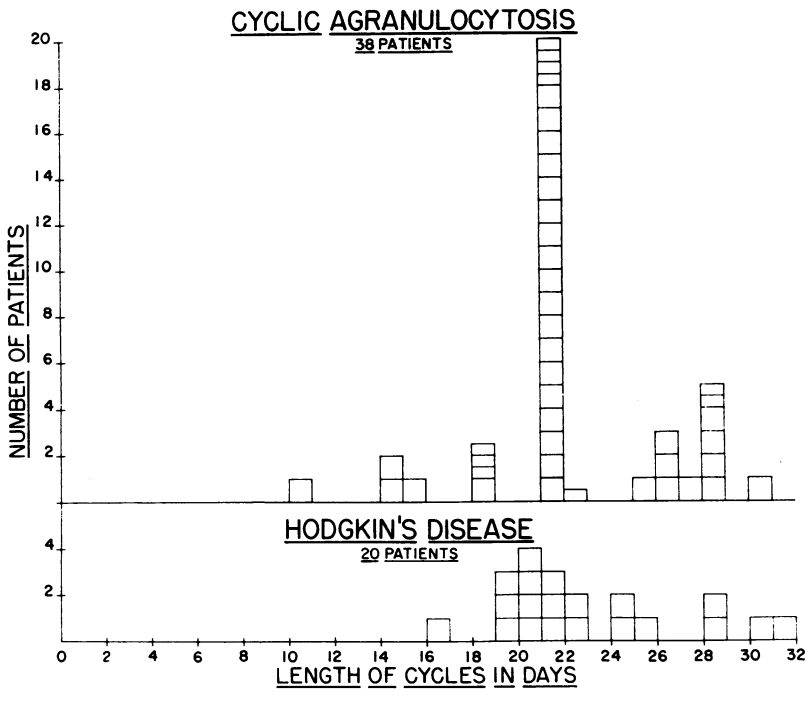


FIG. 20.—(Top) Distribution chart for 38 patients with cyclic agranulocytosis. Abscissas give lengths of cycles in days, ordinates number of patients with each length of cycle. (Bottom) Distribution chart for 20 patients with Hodgkin's disease.

peak at 20 days. Here again we are led to assume some mechanism in the body functions at this rate. The lymph glands and spleen are the organs most obviously affected in these patients; they are also the organs specifically involved in the production of lymphocytes. We would, therefore, expect to find the clock controlling Hodgkin's disease located in these tissues. Of interest here is that the life span of lymphocytes has been calculated to be 20–21 days,[19] which coincides almost exactly with the units of the postulated clocks.

Figure 21 shows the distribution curve for the cycle duration of 31 catatonic-

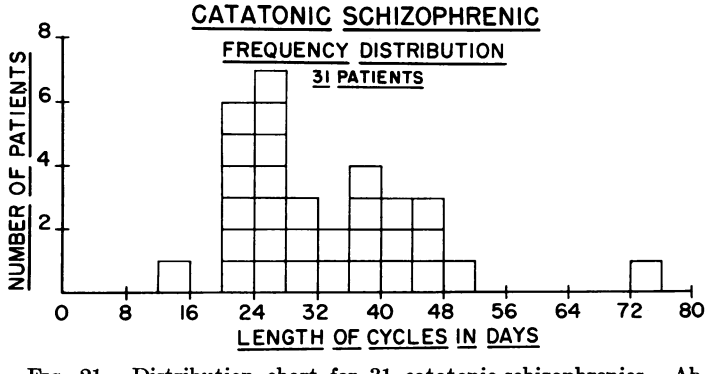


FIG. 21.—Distribution chart for 31 catatonic-schizophrenics. Abscissas show length of cycles in 4-day periods; ordinates number of patients with length of cycles falling within each 4-day period.

schizophrenic patients. As before, the abscissas give the average length of cycle for each patient. The lengths of the cycles for any one individual tended to remain quite constant. Here again we see a delimited distribution, only one patient with a cycle length below 20, and only 2 above 48 days. It seems reasonable to assume that there is a mechanism within the body which in different individuals functions at different levels within this range. The finding that most of these patients responded to administration of thyroid powder, thyroxin, or triiodothyronine[13, 20-23] suggests that a deficiency of circulating thyroid is important in the development of this illness. This is also suggested by our finding that very similar cycles of spontaneous activity, food and water intake, have been produced in rats by removal or destruction of large parts of the thyroid; further that treatment of these animals with thyroid preparation eliminated the abnormal cycles.[24, 25] Noteworthy also is that on the basis of daily observations of follicles of thyroid tissue auto-implanted to the ear of rabbits, Williams[26] reported many years ago that the individual follicles undergo regular cyclic changes. The longest cycle was found to be 20 days.

Figure 22 shows the number of psychiatric patients (108) whose cycles had

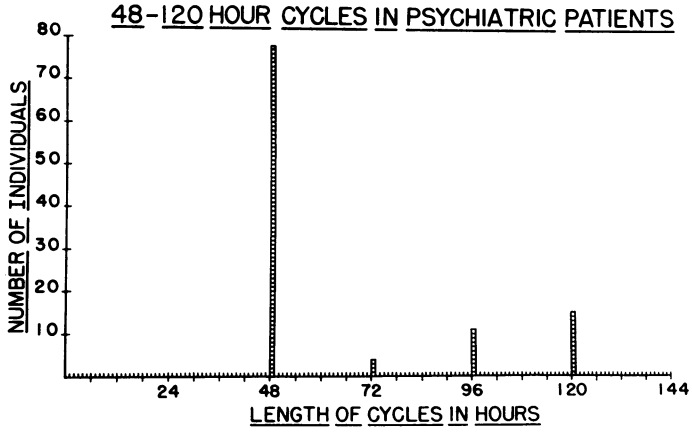


FIG. 22.—Distribution chart for 108 psychiatric patients with length of cycles of 48, 72, 96, and 120 hours respectively.

lengths falling respectively at 48 hours (78 patients), 72 hours (4 patients), 96 hours (11 patients), 120 hours (15 patients). Therefore we might expect also to find mechanisms within the body functioning at these rates. According to their histories many of these patients have suffered severe head injuries, illnesses with high fever, great stress in one form or another. They showed a variety of corresponding cyclic autonomic disturbances in pulse rate, hours of sleep, blood chemistry, appetite, thirst, etc. Thus, it seems likely that the clocks involved may be located in the hypothalamus, which is the site of the nuclei controlling these functions. Head trauma seems apt to be followed by symptoms occurring in 48-hour cycles, while lethargic encephalitis is more often followed by 120-hour cycles.[27]

It must be pointed out here again that evidence at hand indicates that an individual may display symptoms of the presence of several clocks at one time. We have already seen instances in which a patient with intermittent hydrarthrosis

harboured a clock in each of two or three or more joints, each clock measuring time in its own unit. We have also seen instances in which individuals displayed the presence of several different types of clocks—in one case an 18-day cycle of neutropenia and a 34-day cycle of menstruation. There are other instances in which individuals have shown three or more such different types of clocks, for instance a 9-day swelling of the knees, a 7-day cycle of abdominal pain, and a 14-day cycle of renal disturbances. In such patients the peaks of body temperature may not show any obvious periodicity, thus giving the impression of a noncyclic phenomenon; however, plotting of the various specific symptoms that accompany the nonspecific fever peaks often bring out clearly the presence of several independent cycles.

## THREE TYPES OF BIOLOGICAL CLOCKS

In reviewing all the data collected in these patients with various kinds of cyclic disturbances in behavior, mood, and metabolism, it appears that the human body harbours at least three different types of biological clocks:

Type I: *Peripheral Clocks.*—These are located, for instance, in the synovial fluid-producing tissue in the joints, in the cell-producing tissue in bone marrow, etc. They are to a large degree independent of influences arising elsewhere in the organism, particularly in the pituitary gland and the hypothalamus. Thus, for instance, as was mentioned above, cyclic swelling of the joints is generally the only pathological change demonstrable in patients with intermittent hydrarthrosis. There is no fever, no increase in pulse rate, no leucocytosis. Pain may be the only accompanying symptoms. But that these clocks are not completely independent of the rest of the organism is shown by the fact that most of them can be temporarily stopped by pregnancy. However, because of their high degree of independence of other parts of the organism, these clocks are very accurate.

Type II: *Central Clocks.*—These clocks are located in the central nervous system. On the basis of our present knowledge we assume they are most likely to be found in the thalamus, hypothalamus, reticular formation, or in the posterior lobe of the pituitary gland.

I have included the posterior lobe of the pituitary gland as a possible harbourer of a clock, or clocks, of this type, since it actually is part of the brain, and since in animal experiments damage to this structure brought out extraordinarily regular but abnormal cycles in running activity, food and water intake, and functioning of the reproductive tract.[28] From results of our own animal experiments we can conclude that the region of the infundibulum contains more cyclic mechanisms than any other part of the brain or body. But just which structures in this intricate region are the actual sites of such clock mechanisms is not known. Nor do we know to what extent they are controlled through neuro-hormonal secretion in the hypothalamus. At least some of these central clocks keep time with a high degree of accuracy and, again, independently to a large extent of influence from other parts of the body. Thus, as an instance, in one patient a 48-hour clock operated without a miss for over 30 years, despite all the many influences, external and internal, to which he must have been exposed during this time.[29]

Many observations reported in the literature on animals, insects, and plants have established the high degree of accuracy of the functioning of the 24-hour clock, the chief representative of this type of clock.[30–34]

Type III: *Homeostatic Clocks.*—These are part of the homeostatic mechanisms that include the interaction between the target glands of internal secretion—the thyroid, parathyroids, gonads, adrenals, and the anterior lobe of the pituitary gland and/or the hypothalamus. An example would be the ovarian or menstrual clock that depends on the homeostatic relationship between a target endocrine gland, the ovary, and the pituitary and hypothalamus. Another example would be the presumably thyroid clock of catatonic-schizophrenics which would be regulated by the homeostatic mechanism including the thyroid, pituitary, and hypothalamus.

Compared to the Type I (peripheral) clocks and to Type II (central) clocks, these are much less accurate and operate over a much wider range of variation. Thus, for example, the ovarian or menstrual clock measures time most frequently in units of 27–28 days but the length of the units ranges from 14 to 100 days, as may be seen in the distribution chart of the characteristic duration of the menstrual cycles of 1,165 "normal" women (Fig. 23).[35] The ordinates give the number of

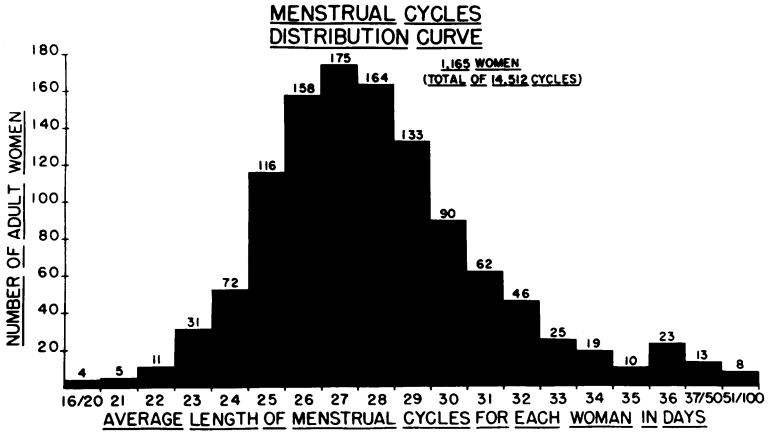


FIG. 23.—Distribution chart of average lengths of menstrual cycles for 1,165 females—a total of 14,512 cycles. (Redrawn from Arey, 1939.)

women with characteristic cycles of each duration (indicated on the abscissas). Similar curves have been obtained by others, both in human beings and monkeys.[36, 37]

In these clocks the actual timing mechanisms are probably located in the target glands but they are very definitely under the influence of secretion from the anterior lobe of the pituitary, as well as being controlled by specific centers in the hypothalamus and thalamus. It is possible that impulses from the sympathetic and the parasympathetic components of the autonomic nervous system may also play a part in the regeneration of this clock mechanism.

*Conditions Under Which These Three Types of Clocks Are Revealed.*—Shock, trauma, and allergy[38] are probably the most common forerunners of the appearance of Type I and Type II clocks. Prolonged spells of fever, prolonged treatment with any one of a variety of drugs or hormones, and presence of arteriosclerosis or of lues have been reported as antecedents of these two types of clocks. However, instances are also on record in which these clocks made their appearance apparently spontaneously.

Particular susceptibility to cyclic manifestations may also play a part since instances are known in which individuals—even within the first few months of life—show evidence of harbouring not only one but several clocks, each measuring time in quite different units, and all independent of one another. This is true especially of the large groups of patients who from early ages suffer from the so-called Mediterranean disease, otherwise known as paroxysmal peritonitis, or periodic abdominalgia.[39] Evidence at hand indicates that this particular susceptibility has a definitely genetic origin, as Armenians and Jews show a high incidence of cyclic proneness and also because, in a number of instances, abnormal cyclic phenomena have appeared in as many as five generations of a family.[40]

In contrast to the other two types of clocks, the usual condition for the appearance of Type III clocks must be either a great reduction of functional activity in the target gland or of the cells of the anterior pituitary that secrete the corresponding trophic hormone. Another possibility which can be anticipated to result in the manifestation of this Type III clock would be consequent upon functional or structural changes in hypothalamic centers resulting from prolonged attempts of the organism to maintain homeostasis in the face of a great reduction in amounts of functioning tissue of the target glands.[24] The results of our studies in experimental production of abnormal cycles of behavior and metabolism in rats indicate that loss of function of the frontal lobes and presumably of the resultant loss of inhibitory influences on lower centers may be followed by the appearance of Type III clocks.[25] The results of these studies on rats have likewise shown that conditions of general debilitation are conducive to the appearance of abnormal cycles.

### TREATMENT OF INDIVIDUALS WITH CYCLIC MANIFESTATIONS OF ILLNESS

It was hoped that light might be thrown on the operation of the clock mechanisms by the study of methods of treatment that have resulted in disappearance of abnormal cycles. However, this study did not reveal much useful information since only a very few effective treatments for any of the cyclic conditions are known. Up to the present time no consistent treatment has been found for patients showing any of the Type I (peripheral) clocks, but a great variety of treatments at different times in one patient or another have resulted in the loss of all signs of the presence of a clock. Thus, for example, in the case of patients suffering from intermittent hydrarthrosis, temporary or permanent cures have been achieved by the following: cauterization of synovial membranes, drainage of the synovial spaces, puncturing or washing out of these spaces with mercuric chloride or carbolic acid, injection of iodine into the synovial spaces, or the oral administration of drugs such as arsenic and quinine.

Many patients showing Type II (central) clocks have made spontaneous recoveries, but to my knowledge none has been helped by any form of treatment.

Symptoms evidencing the presence of Type III (homeostatic) clocks have responded to treatment with thyroid hormone, extract of thyroid, thyroxin, or triiodothyronine. One of our patients suffering from parathyroid deficiency and showing very regular 40-day cycles in mood and behavior lost all signs of periodic changes after treatment with AT-10 and oral ingestion of large amounts of solutions of calcium lactate.

### PATHOLOGICAL FINDINGS IN PATIENTS MANIFESTING CLOCKS

As stated earlier, remarkably few pathological changes have been demonstrated in any patients revealing the presence of biological clocks of any type. Thus, in patients with intermittent hydrarthrosis many examinations of synovial fluid or membranes have yielded very few if any evidences of pathological changes.

The many laparotomies performed in patients with paroxysmal peritonitis have revealed the presence of peritoneal inflammation, but nothing more; inflammation disappeared at the end of each attack.

Examination of the brains of patients with cyclic disorders similarly have not revealed any pathological changes—with the exception of patients with histories of earlier specific central nervous system disorders, such as lethargic encephalitis, progressive paralysis, etc.

### EVOLUTION OF CLOCKS

Evidence at hand indicates that the 24-hour clock—which is found not only in man but in other animals, birds, insects, and plants—is the most primitive clock. How and when the other clocks appeared in different animals, what significance and selective value they had in the life of the animals, remains unknown. It would appear that cyclic phenomena are more readily visible in lower animals than in man. It is possible that, in the process of evolution, clocks that once may have played a part in the animal's life are gradually becoming concealed until in many only two clocks, the 24-hour and 28-day menstrual clocks, are still visible, and that they too may ultimately become concealed, to make their appearance only under various forms of pathological conditions.

In summary, thus far, the results of this study have shown that the body harbours a number of clocks—some located in peripheral organs, for instance in the joints; some located in endocrine glands, for instance the thyroid; some located in the nuclei of the hypothalamus and near-by parts of the brain. It may now be asked how these clocks work; how the various organs of the body undergo such marked periodic changes over long periods of time without showing signs of damage—either on gross or histological examination; how shock, trauma, or other agents elicit cyclic responses; how an assortment of agents may cause the cyclic responses to disappear?

### SHOCK-PHASE HYPOTHESIS

From the prolonged consideration of these questions an idea emerged that may provide an answer to at least some of these questions. This idea came partly from the detailed study of the case histories of the large variety of patients possessing clocks, especially those seen in patients with intermittent hydrarthosis, and partly from the study of a phenomenon that has been observed in the common fruit fly.[41–45] It has been reported that the pupa of the common fruit fly has an inherent 24-hour emergence rhythm; further, that when a large number of pupae are kept together in the absence of any outside stimuli, that is, in constant darkness, at a constant temperature, etc., the flies emerge at all times of the day and night, giving a fairly constant emergence rate until all pupae have emerged; it has further been reported that a shock, short flash of light or thermal stimulus, may serve to bring all of the pupae into phase so that they emerge at 24-hour intervals

until all have pupated. It occurred to me that what happens to the individual members of a colony of flies in response to a strong shock might also happen to the individual units of an organ that are physically closely bound together into an integrated whole. This idea has taken shape as the "shock-phase" hypothesis.

This hypothesis consists of the following postulates:

1. That each one of the functioning units of the organism—cells, follicles, glomeruli, neurons, etc.—has an inherent cycle, the length of which is characteristic of that organ.

2. That these units, although physically closely bound together, may operate independently of one another. Thus, they may all be active, or inactive, or at various stages between activity and rest.

3. That in a normal healthy organ these units function out of phase, that is, some are active while others are resting or at various intermediate stages, thus insuring a fairly constant level of productivity.

4. That under certain circumstances these randomly functioning units of an organ may all be synchronized by a shock or trauma, or by other forms of interference, thus revealing the lengths of the inherent cycles of the individual units.

5. That under certain circumstances the synchronized units of an organ may be desynchronized by various forms of interference, thus restoring the organ to its normal noncyclic productivity.

According to this hypothesis, for instance, the fluid-producing organs of the joints are composed of individual units, each one having its own inherent cycle, ranging in length from 7–14 days. For most individuals the lengths of the cycles of the units are the same in all joints; in other individuals the units within different joints have cycles of different lengths. Under normal conditions some of the units are active, others are resting, others in between, thus maintaining production of a fairly constant amount of synovial fluid from day to day and so concealing all signs of the presence of cyclic phenomena in the individual units. After local injury, allergic shock, etc., the units are brought into phase to produce the great swelling of the joints at 7–14 day intervals. Various forms of nonspecific treatment as was pointed out above, may then desynchronize the units to return the joints to their normal condition.

Further, according to this hypothesis, in normal individuals the neutrophil-producing units in the bone marrow, likewise, have their inherent rhythm of 21, or nearly 21, days, and are capable of independent functioning. Under normal conditions some of these units are producing neutrophils, others are resting, others are at various stages between. Under abnormal conditions these units may all be brought into phase, so that at one time all functioning units are producing cells, at another, none.

According to this theory the same principles apply to: the lymph-producing units in the lymph glands or spleen; the hormone-controlling neurons of the various nuclei in the brain stem; likewise the acid-producing cells of the gastric mucosa; or to the fluid-producing cells of the peritoneal membranes in the abdominal and thoracic cavities, etc.

*Evidence for Hypothesis.*—At the present time we know of a number of organs the functioning units of which may under normal conditions be in all stages of activity, some very active, some completely inactive, the others at various stages between.

It is a common observation that the follicles of the thyroid in a normal animal or person are at any one time apt to be in all stages of activity and rest, and that under pathological conditions they may likewise all be in a state of hyperactivity, or in a state of complete inactivity. In his studies on follicles of autotransplants of thyroid tissue, Williams found that individual follicles pass through definite cycles of growth—and quite independently of one another.[26]

It is known on the basis of studies of the activity of the cells of the gastric mucosa made by means of special dyes that these cells at any one time may be at all stages of activity and inactivity.[46]

Further, it is known that the uterus of normal females shows all stages of activity and inactivity and independence of the rest of the organism.[47]

Some evidence at hand indicates that the glomeruli of the kidneys may likewise function quite independently of one another.[48] However, we have no idea whether the glomeruli have an inherent cycle, and if so of what length.

Evidence is also at hand indicating that the individual neurons of the various centers of the brain may function independently of one another.[49]

## SUMMARY

1. Human beings harbour many clocks—far more than hitherto has been suspected, most of which manifest their presence only under pathological conditions.

2. These clocks may manifest their presence either through physical signs or symptoms, involving in one individual or another almost every organ of the body, or in primarily mental and emotional symptoms, involving almost every form of abnormal behavior, or mood, and thinking.

3. The clocks show an apparent degree of independence of all external physical influences—temperature, humidity, barometric pressure, etc.—as well as of day-to-day emotional situations or disturbances, and so depend on inherent mechanisms.

4. These various clocks keep time in units that range in length from 12 hours to several years; but for each clock the units tend to remain quite constant.

5. Our records indicate the existence of three types of clocks:

I. Peripheral—those located for instance in the blood-forming tissues in the bone marrow, etc.

II. Central—those located in the brain, particularly in the hypothalamus and reticular formation.

III. Homeostatic—those mechanisms involving target organs, endocrine glands, the pituitary, and hypothalamus.

6. A "shock-phase" hypothesis in agreement with the observed clinical phenomena has been proposed to explain how the clocks work. It is assumed that the functioning units of every organ of the body—cells, follicles, neurons, glomeruli, etc.—have an inherent cycle, characteristic of the organ. Under normal conditions these units of any given tissue function out of phase; under abnormal conditions they may function in phase, thus disclosing the length of the inherent cycle of the organ. The units may be put in phase by shock, trauma, allergy, etc.; similarly, they may be put out of phase again by a variety of agents and forms of treatment.

7. Patients with cyclic phenomena offer an excellent opportunity for the

study of the physiology of individual organs as well as of the functioning of the total organism, particularly as seen in various abnormal mental and emotional conditions.

* This material was presented in part in the Thomas Salmon Lectures delivered in New York City, December 2, 1959. The published lectures give a full account of our observations of biological clocks not only of man but of animals; much of the present material was presented in a symposium on "Biological Clocks" organized by the Long Island Biological Laboratories and held at Cold Spring Harbor in June, 1960. Drs. E. A. Park and K. K. Rice made many helpful criticisms and suggestions.

† Studies carried out under grants from the National Institute of Public Health and the National Science Foundation, and through the opportunities offered by a year's membership at the Institute for Advanced Study in Princeton, New Jersey, 1957–1958.

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