395 minutes. The short sleep group had less sleep in combined stages 0 and 1 than the long sleepers ($P < .01$) and probably less than the control group ($P < .05$). They had less stage 2 sleep than either the long sleepers or the control group ($P < .01$), and less stage 3 sleep than the control ($P < .01$). The long sleepers had more stage REM and stage 2 sleep than either the short sleep group or the control group ($P < .01$). They probably had more combined stage 0 and stage 1 sleep than the controls ($P < .10$). The short sleep group did not differ statistically from the control group in stage 4 and stage REM. The long sleep group did not differ from either the control group or the short sleep group in stage 4 sleep. All statistical tests are two tail tests of the *t*-test for independent means.

Subjects selected on the basis of naturally occurring long and short sleep patterns gave evidence of different kinds of sleep processes when these processes were measured in the laboratory and indexed by EEG sleep stages. Short sleepers showed a pattern that may be interpreted as more "efficient." Less time was spent in light sleep and awakenings. Their reduced stage 3 suggests that they made the transition from stage 2 to stage 4 more readily, since stage 3 is essentially a mixed stage 2 and stage 4 record. They received as much stage 4 or REM sleep, generally considered as need states, as did the unselected sleepers, although they slept 1 hour and 15 minutes less. On the other hand, the long sleep group showed marked increases in REM sleep and in stage 2 sleep when compared with the control group, increases of 53 and 36 percent, respectively. The large relative increase in stage REM would reflect a continuation of the intrasleep cycling previously noted, in which REM occurs as a prominent aspect of the later part of the natural sleep process.

Jones and Oswald have recently reported the sleep stage characteristics of two subjects who had consistently slept only about 3 hours per night over a long period of time (*9*). In both cases the absolute amount of stages 3 and 4 constituted approximately 50 percent (80 to 90 minutes) of sleep periods that averaged 165 minutes; REM sleep, on the other hand, occupied only about 40 minutes of the sleep periods. These data indicate that there is a point at which shortening of the total time available for sleep will result in REM restriction in chronic sleep patterns.

Both our data and those of Jones and Oswald support a hypothesis that the absolute amount of REM will be a function of the length of time of the sleep period. In order of sleep length the average amounts of REM in the four populations examined were: 2 hours and 45 minutes sleep, 48 minutes REM (see *9*); 6 hours and 17 minutes sleep, 96 minutes REM (short sleepers); 7 hours and 32 minutes sleep, 101 minutes REM (control group); and 9 hours and 26 minutes sleep, 155 minutes REM (long sleepers). There is some evidence to support the hypothesis that initial "strength" of the stage 4 response is a function of the time between sleep periods. It has been previously noted that a strong stage 4 response is typical of total deprivation conditions exceeding 24 hours (*10*). In the Jones and Oswald study, stages 3 and 4 constituted 50 percent of sleep with 21 hours between sleep periods. This tendency for a potent stage 4 response had been noted in a study of partial sleep deprivation in which sleep was restricted to 3 hours per night (and hence 21 hours between sleep periods) (*3*); stage 3 and 4 sleep constituted 55 percent of the 3 hours. Compared with the long sleepers, the short sleepers of this study (with a longer time between sleep periods) showed a higher stage 4 response in the early part of the night (Fig. 1).

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16 January 1970

## Hormonal Effects on Ontogeny of Swimming Ability in the Rat: Assessment of Central Nervous System Development

Abstract. *The maturation of swimming behavior and the evoked cortical response to sciatic stimulation were studied in newborn rats receiving thyroxine or cortisol. Compared to that of controls the maturation of swimming is accelerated or delayed 2 to 3 days by thyroxine or cortisol treatment, respectively, and this corresponds to ontogenetic shifts in the characteristics of the evoked potential. Front leg movement during swimming normally diminishes at about 16 days of age and is inhibited by day 22. Thyroxine also advances and cortisol delays the age at which this inhibitory mechanism becomes evident, and compresses (thyroxine) or expands (cortisol) the time interval over which it becomes functional. During early postnatal life certain circulating hormones can affect the rate and chronology of central nervous system maturation. Swimming behavior may be a simple model to use in studies concerned with factors affecting the functional and behavioral development of the central nervous system.*

At birth the rat is a very immature organism, and many of the coordinated physiological mechanisms so essential for adult survival do not function effectively (*1*). In addition to perinatal homeostatic immaturity, numerous adult behavioral adaptive mechanisms also develop slowly; for example, the infant rat exhibits no startle reflex (*2*) or righting reflex (*3*). In experiments designed to study learning ability in the infant rat we accidentally observed that, for the first 10 days of life, the infant rat was unable to swim with a coordinated capability. We have found no systematic reports on the maturation of swimming ability in the laboratory rat (*4*).

We have observed (*5*) that administration of thyroxine to the newborn rat accelerated biochemical, neurophysiological, and behavioral development of the central nervous system (CNS), whereas administration of cortisol delayed CNS development. Swimming represents an adaptive response to a life-threatening situation that requires the smooth integrated organization of a co-

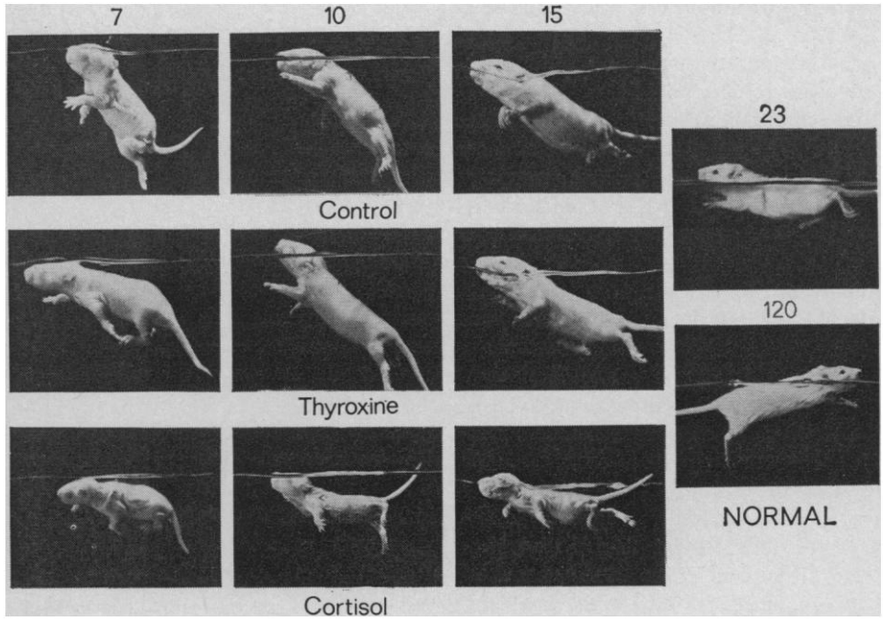


Fig. 1. Maturation of swimming behavior patterns in normal and hormone treated rats. Numbers refer to the age of the animal in days. Note progressive tendency to maintain nose above water and extensor-flexor position of front legs in animals up to 15 days of age. This contrasts with the parallel front leg extension in control untreated 23- and 120-day-old animals.

ordinated series of reflex responses, for example, the righting reflex, vestibular reflexes, and extensor-flexor reflexes; these reflexes are generally studied in isolation from any organized behavioral framework. Swimming ability thus serves as a more complete biological model with which to analyze the development of the neural substrate and its plastic pluripotential.

We now describe (i) the normal maturation of swimming behavior in the rat and its correlation with neurophysiological ontogeny of the sensorimotor cortex and (ii) the effects of neonatal cortisol or thyroxine administration on the development of this behavior.

All experiments were performed on rats of the Sprague-Dawley strain that were bred in our laboratory. A total of 126 rats of both sexes were used. Swimming tests were carried out from day 6 to 23 and on 120-day-old rats; the test consisted of dropping each rat from about five times its own height into an aquarium (47 by 51 by 41 cm). Water was maintained at 27°C and was deep enough so that no part of the rat could touch bottom. The youngest rats (younger than 10 days) were left in the water for 2 to 10 seconds. Although we initially attempted several rating systems (body angle relative to water surface, swimming velocity, locomotor coordination), we subsequently found that, when the rat's nose was maintained above water, neuromuscular coordination was developed and body position was well adapted to effective swimming.

Performance was scored on an arbitrary scale (0, +1, +2, +3), as judged by the nose position, indicating the progressive tendency to keep the nose out of water. The most immature or poorest swimmers were 0, while +3 corresponded to the fully developed juvenile swimming pattern. In that we observed that adult rats, in contrast to infant and juvenile rats, do not use their front legs while swimming, an additional rating scale (4,3,2,1,0) of relative front leg activity was also employed to show the progressive inhibition of such movements. After being tested, each animal was removed from the water and placed in a drying cage before being returned to its home cage. During swimming tests photographic records were also taken.

Thyroxine sodium (1 $\mu$g/g) was administered intraperitoneally on days 2, 3, and 4 to 24 infant rats. Another group of 24 rats received a single injection of cortisol acetate (0.50 mg) on postnatal day 1. Untreated rats, handled briefly, served as controls ($N = 24$).

Evoked potentials in the sensorimotor cortex response to sciatic nerve stimulation were recorded on days 6, 9, 12, 15, 18, and 120; 54 rats were used in this experiment (*6*).

The behavior in the water of all animals less than 6 days of age usually consisted of uncoordinated swimming motions. Most of the rats floated motionless, remaining entirely or partially submerged, arching their backs, and showing hyperextensive reflex activity of the extremities and toes. Because their noses were below the surface of the water, the animals had to be removed to prevent their being drowned.

Control animals from 6 to 15 days of age showed a progressive tendency toward achieving better coordinated movements (Figs. 1 and 2). At the beginning of this period (day 6), animals were able to maintain their equilibrium but showed poorly coordinated flexor and extensor movements that were not sufficient to directionally propel them; they frequently swam in circles or exhibited random directionless movements. At 7 days of age, the rats showed a beginning of flexion and contralateral extension of the legs, associated with rudimentary attempts to climb the wall of the tank; at 8 days, turn-around movements were successively appearing, and these mainly involved the front feet. However, at this age animals were still unable to maintain their noses out of the water. By 10 to 12 days of postnatal life well-developed sequential flexion and extension of front legs occurred. At 15 days coordinated movements of all four legs were seen. From 12 days onward, the rat kept the nose, face, and a part of the head out of water.

In the thyroxine treated group, the same sequence of maturation was observed, except that it was advanced by 2 to 3 days as compared with controls (Fig. 1). In cortisol treated rats, there was a remarkable retardation in the normal development of the motor pattern for swimming (Fig. 1). Uncoordinated circle movements, whether floating or submerging, remained until about 9 days of age. When the animals were able to display coordinated movements they looked anxious or excited, showing faster movements to escape than controls. Furthermore, they were unable to keep their noses out of the water until about 15 days of age. Figure 2 indicates that thyroxine and cortisol influenced not only the age at which swimming began but also the rate at which it progressed to a mature pattern. Thus development of swimming capability in the normal rat encompasses

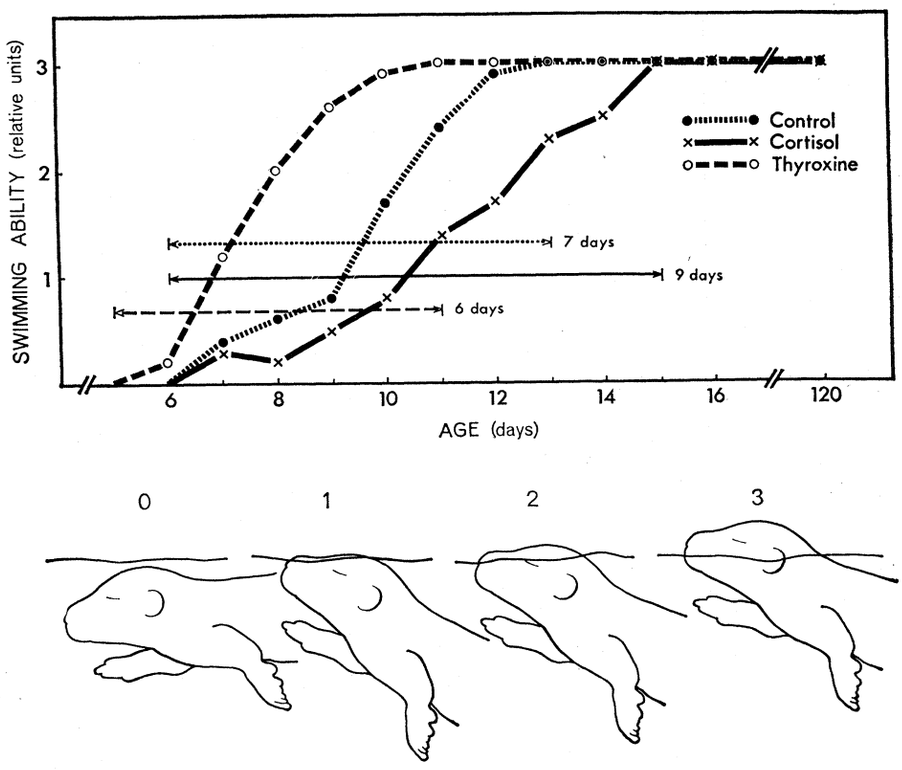


Fig. 2. Graphic representation of maturation of swimming ability in normal and hormone treated rats (see text) at different ages. Drawing illustrates the criteria used to ascribe arbitrary rating units to swimming behavior. The number of days over which swimming behavior assumed stable characteristics is indicated by the horizontal lines.

days 6 to 12 (7 days) and in thyroxine and cortisol treated animals, days 5 to 10 (6 days) and days 6 to 15 (10 days), respectively (*7*). The characteristics of foreleg movements indicate a similar pattern; initially (days 6 to 8) they are rapid, random, and uncoordinated. By days 9 to 10, crossed extensor movements are present; up to 15 days of age, foreleg activity becomes progressively better coordinated and effective and plays an important role in juvenile swimming behavior.

With increasing age of the animal, changing patterns of foreleg movement during swimming were unexpected and warrant special comment. Surprisingly, at about days 15 to 16, characteristics of this activity change, becoming more random and irregular; by day 22, activity ceases and the forelegs are held continuously in extension as in the adult pattern (*8*), as shown in Figs. 1 and 3. This period of progressive cessation of foreleg activity lasts 7 days in control rats, from days 16 to 22. The development of swimming behavior and the mechanism governing foreleg rigid extension may be related to the neuroanatomical changes taking place in the cerebellum and cortex during this time (*9*, *10*). Thyroxine not only advances the age over which these inhibitory changes occur (days 15 to 20) but compresses the time interval (or accelerates the rate) within which they develop (6 days). In the cortisol treated rats foreleg movement was maintained, as in the controls, until about day 16; however, the period of progressive inhibition was considerably prolonged (10 days), until day 25 (Fig. 3). These results can be correlated with previous behavioral studies, indicating that 35-day-old rats that received thyroxine as infants do not perform as well on certain learning tasks as untreated controls. However, as infants they acquire a conditioned avoidance response more rapidly (*5*). We suggested (*5*) that compressing CNS development into a shortened temporal-experiential interval may prematurely limit its later behavioral flexibility.

The maturation of sensorimotor cortex evoked potential response to sciatic nerve stimulation is accelerated by treatment of newborns with thyroxine and delayed by treatment with cortisol (Fig. 4) (*11*). These effects on development correspond closely to effects on swimming behavior. The accelerated development of swimming capability and sensorimotor cortex evoked potentials in thyroxine treated rats suggests an underlying relation to the morphophysiological properties of the cerebellum

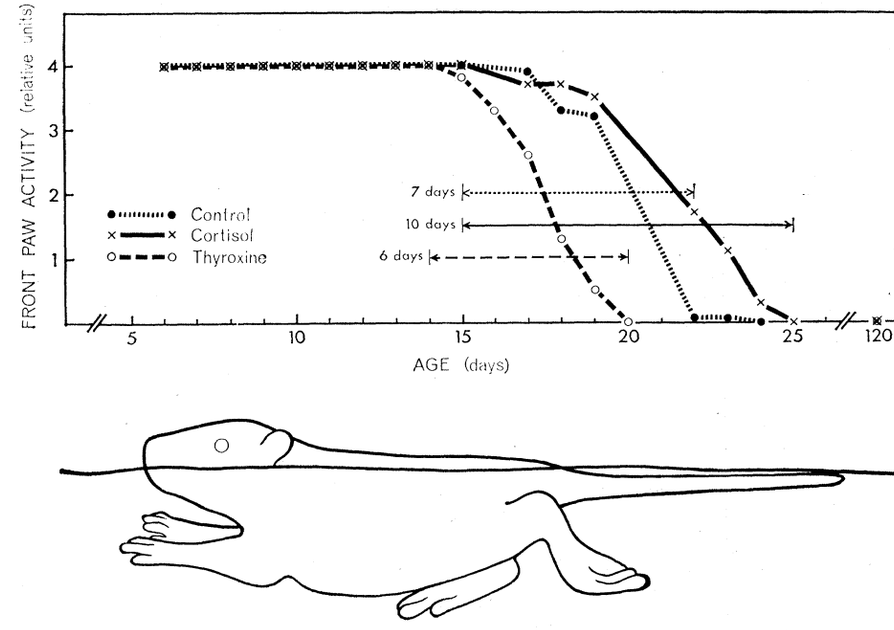


Fig. 3. Graphic representation of changing characteristics of front leg activity during development of normal and hormone treated rats. Drawing illustrates swimming position of front feet of normal adult rat and would correspond to a relative score of 0. The numbers of days from the beginning to the end of the progressive inhibition of front leg activity is indicated to the left of the horizontal bars.

and cerebral cortex. Data on cortisol treated animals indicate a severe retardation of integrative sensorimotor mechanism development as well as of swimming coordination and capability. Effects of cortisol on the development of cerebellar tissue have not yet been described; however, our results support the conclusion that a disturbance and delay in its functioning and maturation has occurred.

These experiments give clear evidence that the hormonal environment during early stages of neuronal development can modify the normal ontogeny of the complex integrated neuromuscular adaptive mechanisms involved in swimming. It is well known that the cerebellum through its interconnections with cortical and subcortical structures, modulates these sensorimotor and neuromuscular effector systems, in order to effectuate smooth, well-directed movements. Our data are in agreement with observations (*9*) indicating that growth of the cerebellum and its microneurons is slowest during the first 5 days of postnatal life, that cell differentiation is absent, and that few of the folia are formed. Furthermore, myelinization in the rat brain starts in the cerebellum at 8 days of age, and in the gracilis, cuneatus, and pyramidal tracts at about 3 and 6 days of age, respectively (*12*).

Reflexes involved in space orientation, posture, voluntary movement, and equilibrium are integrated largely in labyrinthine (*13*) and cerebellar centers. Head and nose patterns involved in swimming are a component of these reflexes, and they are presumably not fully integrated in normal rats before day 12. Effective patterns of head-nose orientation appear by day 10 in the rats treated with thyroxine and by day 15 in those treated with cortisol. In both cortisol and thyroxine treated animals, eye-opening was advanced 2 to 3 days. Advanced age of eye-opening in the cortisol group is associated with a retarded development of swimming and of the CNS, whereas in thyroxine treated animals, it is associated with an accelerated age of swimming and CNS maturation (*5*, *6*). Age of eye-opening has been frequently used as an indication of more rapid CNS development that follows neonatal handling (*14*), and our results indicate that this is not a reliable criterion.

The hormonal climate during the early postnatal period affects the rate of maturation of the rat's brain responsiveness to environmental stimuli (*6*). Our data now provide additional information that parameters in the internal environment (hormones) can interact with the CNS in the early stages of life and can modify the development of the morphophysiological properties of the neural substrate. It also suggests that swimming and its development may be a productive model to use in studying functional integration of the multitudinous component reflexes, usually studied in isolation, that enable the organism to effectively adapt to its environment. A study of factors affecting swimming and its pattern of development may provide insight into the functional ontogeny and ecology of adaptive systems in general.

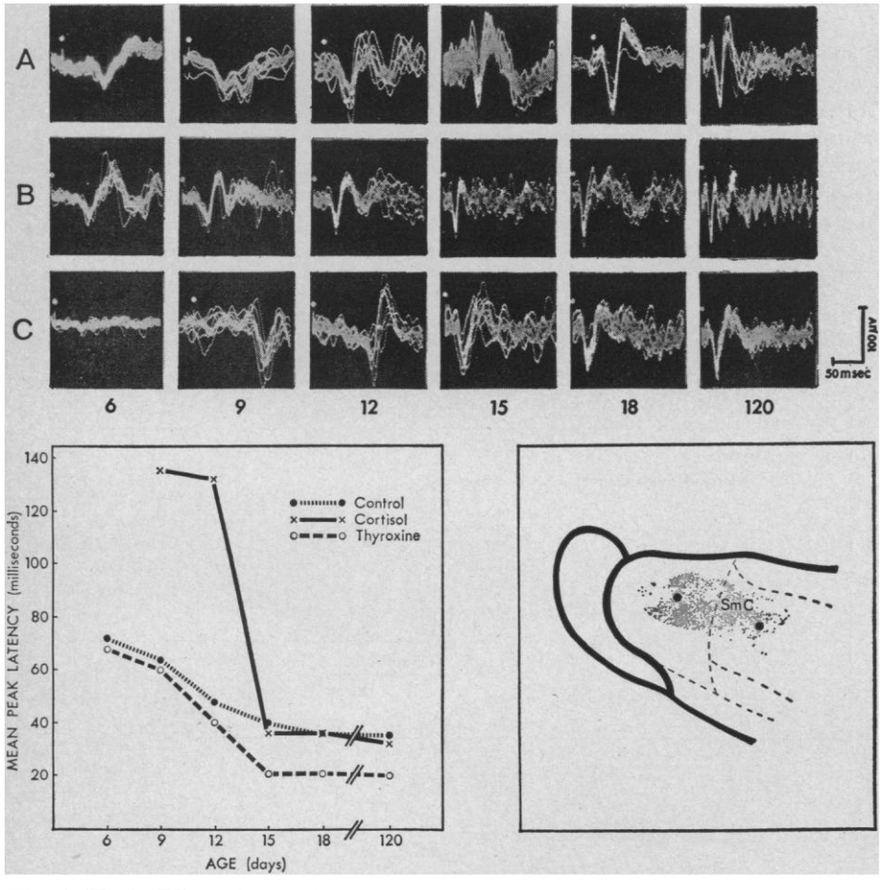


Fig. 4 (Top). Effect of administration of thyroxine (B) and cortisol (C) to newborns on the maturation of the evoked potential of the sensorimotor cortex response to sciatic nerve stimulation. Normal pattern of evoked potential development is shown in (A). In the graph (bottom left) are shown differences in latency of evoked responses ('white dots indicte time of stimulation); (bottom right) the anatomical location from which consistent recordings were obtained.


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4. We have been able to find only two reports dealing peripherally with development of swimming behavior in mi→ J. A. King, *Anim. Behav.* **9**, 142 (1961) studied swimming speed in young deermice of different subspecies, a→ W. M. Fox, *ibid.* **13**, 234 (1965), observed that until 6 to 8 days of age mice swim in circles and as they get older they tend to swim in a straight line.
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6. M. Salas and S. Schapiro, *Physiol. Behav.*, in press. Taped records of animals up to 12 days of age were revisualized on an oscilloscope, and the first ten consistent responses were superimposed and photographed, and mean peak latency was measured and graphed. From day 15, records were consistent and responses to be superimposed were chosen at random.
7. The body weights of the cortisol treated animals were less than that of controls. [S. Schapiro, *Proc. Soc. Exp. Biol. Med.* **120**, 771 (1965)]. This cannot of itself ac-

count for swimming behavior differences, for thyroxine treated animals were also lighter than the controls although somewhat heavier than the cortisol group. In general, each rat was studied longitudinally and therefore prior swimming experience may have influenced the timetable of swimming development. Recent longitudinal as opposed to cross-sectional studies suggest however that this is not the case.

8. The front feet are held relatively immobile in parallel extension and are used only for climbing escape attempts or pawing at the glass or periodically to aid in turning. A preliminary test of the adult mouse and gerbil indicates that they also swim with front paws in inactive extension. However, adult rabbits and hamsters, like dogs and cats, use their front feet actively in contralateral extensor-flexor movements. Phylogeny of these species differences may relate to relative front limb specialization as it equips an animal to function effectively in its own ecological niche.
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11. Control rats displayed long latency, monophasic, positive responses from the earliest time period analyzed. There is a progressive reduction of mean peak latency with age, and the waveform gradually changes to a biphasic configuration, attaining adult patterns when the animal is 18 days old. From 12 days onward, secondary slow waves appear after primary responses. In thyroxine treated rats a better configuration, shorter latency and biphasic responses, followed in most of the cases by slow waves, were obtained in all ages. These responses exhibited adult characteristics at 15 days of age, although even shorter latencies were still demonstrated at 18 and 120 days of age. In cortisol treated animals, evoked responses at 6 days of age were rarely seen. Consistent monophasic responses of longer latency than those of controls appeared at 9 days and progressively reduced their latency, displaying the same biphasic waveform and latency of the control by day 15.
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13. The structures controlling the integrated movements of swimming are unclear. Partial or total cerebellectomy, while completely disrupting coordinated antigravity movements may only slightly impair effective swimming in the adult dog. Labyrinthine structures appear to primarily coordinate swimming reflexes: R. S. Dow and G. Moruzzi, *The Physiology and Pathology of the Cerebellum* (Univ. of Minneapolis Press, Minneapolis, 1958), pp. 25, 27, 39, 101, and 273.
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15. Supported in part by PHS grant AM-06603, and by a fellowship to M.S. from the Foundation Fund for Research in Psychiatry. We thank Dr. Joseph Altman for discussion of the manuscript.

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13 November 1969; revised 2 January 1970

## Water: Nomenclature

Lippincott, Stromberg, Grant, and Cessac (*1*) published further experimental confirmation of the existence of orthowater and proposed that the species be renamed "polywater." Normally I regard nomenclature as a rather trivial scientific matter, but in the present instance considerable confusion could result if the proposed name is adopted. While it has a certain popular ring to it, the name "polywater" is equally applicable to any of a number of possible water species found in pure water, in solutions, and near interfaces, as well as to the species whose formation appears to be catalyzed by silica surfaces. The polymeric nature of liquid water, it should be noted, has been recognized since the 19th century (*2*). "Ordinary" water, therefore, can be accurately described as "polywater."

Alternatively I would like to propose the following system of nomenclature which represents an extension of the usage of Bernal and Fowler (*3*) and parallels the accepted usage for the solid phase:

| | |
|---|---|
| In the bulk, pure liquid | |
| Water-i | The monomer |
| Water-ii | Small polymers $(H_2O)_n$ of $n = 2$ to 4 |
| Water-iii | Large polymers of $n > 4$ |
| | a. Randomly hydrogen-bonded |
| | b. Hydogen-bonded with at least non-ice-I-like near-neighbor order |
| Water-iv | Ice-I-like |
| Near solutes | |
| Water-v | Electrostricted water of hydration |
| Water-vi | Enforced water structures near ions (except water v) |
| Water-vii | Broken water structure near ions |
| Water-viii | "Icebergs" or clathrate structures near nonpolar solutes or nonpolar segments of macromolecules |
| Near interfaces | |
| Water-ix | Near neutral and nonpolar interfaces |
| Water-x | Near silica |
| Water-xi | Absorbed or chemically bound water |

In the foregoing system "polywater" or orthowater is designated water-x.

In order to avoid the implication that these forms represent phases in the thermodynamic sense, in contrast to the case of the ices, lower rather than upper case Roman numerals have been used. The proposed scheme is a tentative working one, its categories may be replaced by more exact designations if and when the nature of the water species becomes more exactly identified. While systematic, the scheme is flexible —an important advantage for, in the light of subsequent studies, some of these species may be found to be nonexistent in the liquid (i, ii, and iv), some may be found to be synonymous (iii and iv; iii and vi; viii, ix, and x), and some may be further subdivided (xi); but the usefulness of the above proposed nomenclature should remain unimpaired.

Although not repeated in the above scheme, a given water species may occur in more than one of the three location categories: water-iv, for example, may be found in bulk solution, near solutes, and near interfaces; water-v, -vi, and -vii will surround charge sites on a surface as well as ions in solution; and according to Lippincott *et al.* water-x may exist in bulk solution as well as near silica surfaces.

The proposed system provides very brief, yet exact, descriptions of the various theories of water (the Bernal-Fowler theory becomes a water-$iii_b$–water-iv model; the Frank-Wen-Nemethy-Scheraga theory a water-i–water-$iii_a$ model; the Pauling-Frank-Quist theory becomes a water-i–water-viii model; the Samoilov theory a water-i–water-iv model). It also describes complex situations, such as those obtaining in inorganic ion-exchangers (water-v–water-vi–water-vii–water-x–water-xi) and biomembranes (water-viii–water-ix–water-xi).

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17 November 1969

## Sex Ratios of Newborns and Schizophrenia

F. T. Melges (*1*), referring to my article (*2*), introduces new data from a previous report (*3*) which fail to show a relationship between the sex of newborns and mothers who develop postpartum schizophrenia. I have confirmed my findings and have, in collaboration with R. Levine, used an elaboration of my early speculations to predict successfully the sex of 44 of 47 infants, prediction based upon the history and course of the maternal mental illness (*4*).

In his report Melges utilizes the broad diagnostic criteria that I described, and in a personal communication states he ran "a separate analysis