

Joseph Knoll: Enhancer Sensitive Brain Regulations and Synthetic Enhancers (Selegiline, BPAP) Which Counteract the Regressive Effects of Brain Aging

## Chapter 4

### **The peculiar physiological role of the catecholaminergic neurons to keep the brain in a continuously active state**

There are substantial reasons to assume that catecholaminergic neurons keep the higher brain centers continuously active and care for changes within broad limits, according to need. As signaled by the appearance of the EEG in an early phase of development, the catecholaminergic brain engine, responsible for the integrative work of the central nervous system (CNS), is ignited once spanning for a lifetime.

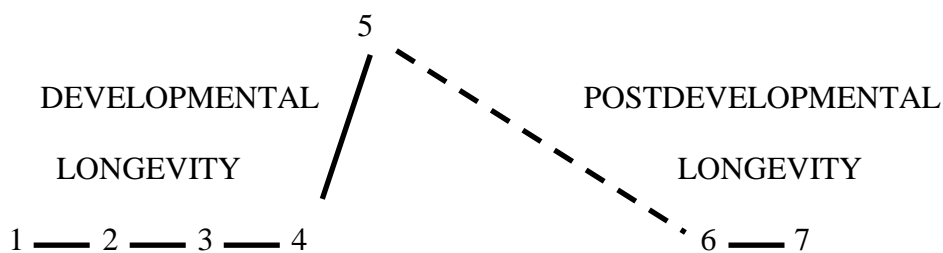
Due to aging, the maximum level of activation of the CNS, via the catecholaminergic system, decreases progressively over time. The blackout (“natural death”) of the integrative work of the CNS, signaled by the disappearance of EEG, occurs when the catecholaminergic system’s ability to activate the higher brain centers sinks below a critical threshold and an emergency incident transpires, when a high level of activation that is needed to survive and the CNS can no longer be properly activated. This explains why a common infection, a broken leg, or any other normally minor challenge given fully active catecholaminergic machinery may cause death in old age.

The essence of this hypothesis is depicted in the Figure below. According to this schema the life of a mammalian organism can be divided, from a functional point of view, into six stages, each beginning with a qualitative change of crucial importance. The first stage starts with the fertilization of the ovum and lasts until the catecholaminergic system properly activates the higher levels of the brain, which then assume the lead and integrates the different parts of the organism into a highly sophisticated entity. The first stage of development of the mammalian organism is completed when the catecholaminergic engine of the brain is put into gear once and for all. This is the intrauterine birth of the unique individual. The appearance of EEG signals the transition from the first into the second stage of development.

Cells need oxygen, water, and food for life. These are first supplied, via the placenta, by the mother. The subsequent, highly complicated evolving process is devoted to ensuring independence from the mother.

The second stage of development ends with the passage of the fetus from the uterus to the outside world. From a functional point of view birth means the transition from fetal to postnatal circulation, with the newborn infant now supplying itself with oxygen.

The third stage lasts from birth until weaning and serves to develop the skills needed for the maintenance of integrity and for the infant to supply itself with water and food.



- 1) FUSION OF THE SPERMATOZOON WITH THE OVUM
- 2) THE INTEGRATIVE WORK OF THE CNS SETS IN;  
APPEARENCE OF EEG
- 3) BIRTH OF THE FETUS
- 4) WEANING
- 5) SEXUAL MATURITY IS REACHED
- 6) THE INTEGRATIVE WORK OF THE CNS BLACKS OUT;  
DISAPPEARANCE OF EEG; "NATURAL DEATH"
- 7) DEATH OF THE LAST CELL

Figure: Conception about essential changes during the lifetime of mammals (Knoll 1994).

The fourth stage lasts from weaning until the supreme goal in nature: full scale sexual maturity is reached. This is the most delightful phase of life, the glorious uphill journey. The individual progressively takes possession, on a mature level, of all abilities crucial for survival and maintenance of the species. It learns to avoid dangerous situations, masters the techniques

for obtaining food and water, develops procreative powers for sexual reproduction and copulates. This is, at the same time, the climax of developmental longevity.

The discovery of the enhancer-sensitive brain regulations revealed that during *the interval from weaning (3<sup>rd</sup> week of life) until the end of the 2<sup>nd</sup> month of age, thus during the decisive period for development, enhancer-sensitive neurons work permanently on a significantly higher activity level than before weaning (in 2-week-old rats)*. We measured the dopaminergic, noradrenergic and serotonergic activities in the brain during the crucial developmental phase, from weaning to sexual maturity (in 4- and 8-week-old rats) and in the early post-developmental phase of life (in 16- and 32-week-old rats). As an indicator of the basic activity of catecholaminergic and serotonergic neurons in the brain, we measured the release of dopamine (DA) from striatum, substantia nigra and tuberculum olfactorium; of norepinephrine (NE) from the locus coeruleus; and of serotonin (SE) from the raphe, in both male and female rats (Knoll and Miklya 1995).

The full, sexually mature individual fulfills its duty. Thus, to maintain the precisely balanced natural equilibrium among living organisms, the biologically “useless” individual has to be eliminated; according to the inborn program, the fifth, post-developmental (aging) stage of life begins. Since, from the discontinuation of breast feeding (end of the 3<sup>rd</sup> week of age) until the appearance of sexual hormones (end of the 2<sup>nd</sup> month of life) we measured in both male and female rats a significantly pronounced enhancer regulation in the dopaminergic, noradrenergic and serotonergic neurons, it was reasonable to deduce that sexual hormones play the key role in terminating the developmental phase of life (Knoll, Miklya, Knoll and Dalló 2000).

The essence of the fifth stage is the progressive decay of the catecholaminergic system’s efficiency during the post-developmental lifespan, until at some point, in an emergency situation, the integration of the parts in a highly sophisticated entity can no longer be maintained and “natural death,” signaled by the disappearance of EEG signal, sets in.

As parts of the organism remain alive, the sixth and last stage of life is the successive death of the different groups of cells, until the death of the last cell.

The hypothesis outlined suggests that quality and duration of life rests upon the inborn efficiency of the catecholaminergic brain machinery, i.e., a higher performing, longer-living individual has a more active, more slowly deteriorating catecholaminergic system than its low

performing, shorter-living peer. To simplify this concept, we may say that a better brain engine allows for a better performance and a longer lifespan.

*The concept clearly predicts that, as the activity of the catecholaminergic system can be improved at any time during life, it must essentially be feasible to develop a technique for transforming a lower-performing, shorter-living individual, to a better-performing, longer-living one. It therefore follows that a shift in the duration of life beyond the technical lifespan with a yet unpredictable limit must be possible in all mammals including the human species (Knoll 1994).*

Because of the special role of the catecholaminergic neurons maintaining the brain permanently stimulated is the condition *sine qua non* for the indefatigability of the human-brain driven by an innate or an acquired drive. It is obvious that the ability to acquire an irrepressible urge for a goal not necessary for survival represents the most sophisticated function in the mammalian brain. Whenever a new drive is acquired, chains of inextinguishable conditioned reflexes are stabilized; neurons responsible for emotions are also coupled to the integral whole. Thus, cognitive/volitional consciousness is necessarily inseparable from an affective state of consciousness. The mechanism that binds emotions, appurtenances to any chain of inextinguishable conditioned reflexes is of crucial importance to interpersonal communication (Knoll 1969, 2005, 2010).

Since the era of enlightenment, the spiritual revolution which resulted in a previously unthinkable acceleration in the development of science and technology, it was foreseeable that the myths-directed first phase of human history is slowly arriving to its chaotic end phase. Dramatic changes since the beginning of the 20<sup>th</sup> century (the Great War, Second World War, Holocaust, as well as the Terror War in progress) are awful warnings that the myths-directed first phase of human history is already unmaintainable and is fortunately slowly approaching its shameful end (Knoll 2001, 2003, 2005).

The ratio-directed future looks promising. Robots will work; science and art remain the main human activities. Thousands of anecdotes recall ingenious scientists/artists working day and night in perfect harmony and satisfaction toward their acquired drives. The higher the percentage of the population who find their best-suited acquired drives to their natural endowments, the better is the quality of life in a ratio-directed society.

The *same basic mechanism* manipulates the behavior of domesticated animals and humans. However, in striking contrast to the human brain with practically unlimited capacity

to fix acquired drives, this ability in animals is strictly limited. In our animal model we manipulated the behavior of our rats to establish the “glass-cylinder-seeking drive.” *Finally, the rat behaved as if possessing a fanatical desire to reach the unnatural goal (Chapter 1). In the properly manipulated rat the unnatural drive suppressed the life important natural drives.* The same applies to human beings. The brain of a suicide killer is furtively manipulated. The properly acquired unnatural drive develops as a result of long-lasting training. The subject always acts under coercion, under severe mental pressure. Nevertheless, it is the nature of acquired drives that if the manipulation was fully successful the individual ultimately behaves as one possessing a fanatical desire to reach the unnatural drive-motivated goal. Thus, the expert-opinion that the global war on terror is a 7<sup>th</sup>-century clash involving 21<sup>st</sup>-century weapons is correct.

Furthermore, since the development of science and technology continually accelerates, no matter how much time is still needed to arrive to the ratio-directed era of human history, *to achieve this final goal of development is a physiological necessity and cannot be stopped.*

Similar to humans, even animals capable of establishing acquired drives work with them passionately and untiringly. *In striking contrast, the innate drive works until the urge is satisfied.* The better we understand the enhancer-sensitive regulations in the human brain, get acquainted with the identity of their natural enhancers and develop proper synthetic enhancers, the better are our chances to counter the regressive effects of brain aging and improve the quality and duration of human life.

*Unfortunately, for the time being, the ability of species to fix acquired drives as the mechanism of the manipulability of mammalian behavior is still not common knowledge. But all is not lost that is delayed.* It is of crucial importance that with brains capable of acquiring drives species appeared whose members could manipulate each other’s behavior and act in concert. This was the condition *sine qua non* for the evolution of social living, a form of life that enabled species to surpass qualitatively the performance of any given individual.

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August 23, 2018