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A Search for the Boss: The Thing inside Each Organism That Is in Charge

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Abstract

It is proposed that every organism is controlled by The Boss. The Boss is in charge of each organism's behavior, metabolism, development, immune response, and reproduction. All organisms have perhaps the same Boss. This is an unknown mechanism. An example is behavior: in people and other primates, The Boss acts at the prefrontal cortex of the brain to direct the behavior of the organism by means of executive function. It is proposed that simpler versions of a prefrontal cortex occur also in other animals and in plants and in microorganisms. Thus The Boss directs the behavior of all organisms.

Keywords: Executive Function; Global Regulators; Biochemistry; Neurobiology; Genetics; Bacteriology

Introduction

This has been a century of great accomplishments in the biological sciences. We have learned a vast amount of what organisms do and how they do it, all the way from microorganisms to plants to animals including humans. But the search for what ties it all together (if anything) has been avoided and the answer is unknown.

"... We can only work in very narrow areas within certain fields. We do not know whether the contemporary road and method will eventually stumble against some fundamental barrier. We only recognize single elements in this puzzle, but the body adds and orders them in a way which is difficult to understand. Occasionally, one [not I] would like to believe that the human intellect is incapable of comprehending the conditions of its own biological functions. In any event, we are ignorant about the fortunes of our hitherto successful approach for the next hundred years and whether entirely new ways will have to be devised in order to continue our physiological studies."–Karl E. Rothschuh "*History of Physiology*" [1].

Here are presented such "entirely new ways" for biology, namely that all organisms have something in charge – "The Boss"

– And that The Boss directs behavior, metabolism, development, immunological response, and reproduction. The Boss may be the same for all organisms.

Behavior, Metabolism, Development, Immunological Response, Reproduction

Behavior and its Control

Behavior in Humans and in other Primates: Starting in the 1870's it became apparent to some psychologists that there is a part of the brain, the prefrontal cortex, that is master of the whole brain; see a review up to 1970 by the neurophysiologist Aleksandr Luria, who himself modernized this concept and studied syndromes resulting from deficiencies of the prefrontal cortex [2]. This part of the brain became known as the "central executive" through the research of the psychologist Alan Baddeley [3] or as the "executive brain" through the research of the neuropsychologist Elkhonon Goldberg [4], a student of Luria's; it is now known as "executive function" or "executive control". For a review see Goldberg & Bougakiv [5] and Sam Gilbert & Paul Burgess [6].

According to the anatomist Korbina Brodman, working in 1906 [Fuster 7], the prefrontal cortex or its analogs account for 29% of the total cortex in humans, 17% in the chimpanzee, 11.5% in the gibbon and the macaque, 8.5% in the lemur, 7% in the dog, and 3.5% in the cat; for a modern version by Joaquín Fuster [7] see Figure 1.

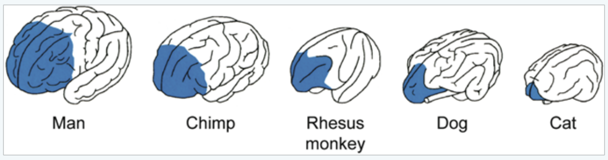

Figure 1. The prefrontal cortex, in blue, according to Fuster [7].

The prefrontal cortex of the brain is compared to that of the chief executive officer of an organization by Catherine Mateer et al [8].

"Imagine the role of the executive officer of a large company, who has overriding control over the company's action. This person sets goals, plans and organizes company activities to meet these goals, and decides when to start to do something, when to stop doing it, when to do something else, and when to do nothing at all... At a basic level, this is what the prefrontal cortex does for humans."

In 1848 a construction foreman, Phine as P. Gage, sufferedfrom an explosion that sent an iron rod through his brain. After the rod was removed, he turned from "the most efficient and capable man into one with new personality traits: fitful, irreverent… capricious and vacillating… he had the animal passions of a strong man."So reports then euro scientist Antonio Damasio in "*Decartes' Error: Emotion, Reason*, *and the Human Brain*" [9]. Hanna Damasio studied Gage's skull and found that it must have been the frontal lobe that was hurt. According to a more recent but similar case studied by Paul Eslinger & Damasio [10] "the frontal lobe of the brain was damaged by a tumor that was removed, resulting in a turn of the patient's emotional reactivity and in impaired ability to reach decisions though retaining a normal intellect. Such cases show that some part of the frontal lobe of the human brain is involved in emotion, reason, and decision-making" [Damasio 9]. See also the classical work of Brenda Milner on removal of parts of the frontal lobe of humans [11]. Milner also studied a patient who had amnesia as a result of a bilateral surgical ablation of parts of the hippocampus [Scoville and Milner 12]. After death his brain was examined: lesions in the hippocampus and in the orbit of frontal cortex were found [Annese et al.13].

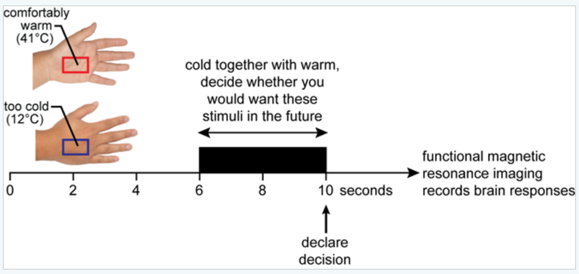

Figure 2. Attractive and repulsive temperatures applied to humans: the role of the prefrontal cortex. From description by Grabenhorst et al. [15].

One function of the prefrontal cortex in humans and other primates is decision making, as reviewed by Jonathan Wallis [14]. An example of the role of the prefrontal cortex in human decision-making is provided by the research of the brain scientist Edmund Rolls et al. [15]. They used functional magnetic resonance imaging to measure the response when a person's hand was exposed to pleasant warmth or unpleasant cold or the two together (Figure 2). When the two were applied together and the subject was asked to decide if he/she would want that again if it were available in the future, there was a response in the prefrontal cortex, but with either stimulus alone, or with the two together without needing a decision, responses were only elsewhere in the brain. These authors came to a similar conclusion when an attractive odor was pitted against a repulsive odor, again in humans [Rolls et al.16].

Another function of the prefrontal cortex in humans and other primates is working memory: knowing what to do even when the stimulus for doing it is removed. "Working memory," reported Patricia Goldman Rakic [17] "is the term applied to the type of memory that is active and relevant only for a short period of time, usually on the scale of seconds. A common example of working memory is keeping in mind a newly read phone number until it is dialed and then immediately forgotten." For a review of working memory in primates see Postle BR [18]. See Eric Kandel [19] for a review of prefrontal cortex and working memory.

What is in Charge of the Behavior of "Simpler" Animals?

Executive control has been reported in rodents, birds, and insects [20-24].The Boss has not been reported.

The animal behaviorist Donald Griffin in "*Animal Minds: Beyond Cognition to Consciousness*" [25] presented evidence that all animals have mentality, and he suggested that zoologists should investigate questions of animal consciousness. He used examples from vertebrates such as dolphins and birds and from invertebrates such as honeybees. But plants and protists are not eligible, Griffin says"...animals are also clearly more than mobile metabolisms. They *act* [sic], that is they do things spontaneously, on their own. The complexity... distinguishes them in an important fashion from microorganisms, plants, and physical systems.… Since protozoa lack anything at all comparable to a central nervous system capable of storing and manipulating information, it seems highly unlikely that they could be capable of anything remotely comparable to conscious thinking."

The central complex of insects is required for sensing attractants and repellents (Figure 3) [26, 27]. The central complex is related to the mammalian brain (Figure 4) [26]. They are derived from a common ancient ancestor [28]. Motile *Drosophila* mutants have been isolated [29] that failed to be attracted by anything tested (Figure 5) and failed to be repelled by anything tested. They have a defect in the mechanism that dictates a behavioral response.

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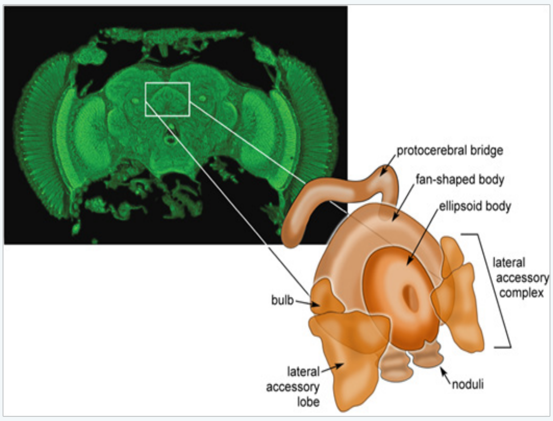

Figure 3. Central complex of the *Drosophila* brain Strausfeld & Hirth [21]; Hanesch et al. [22].

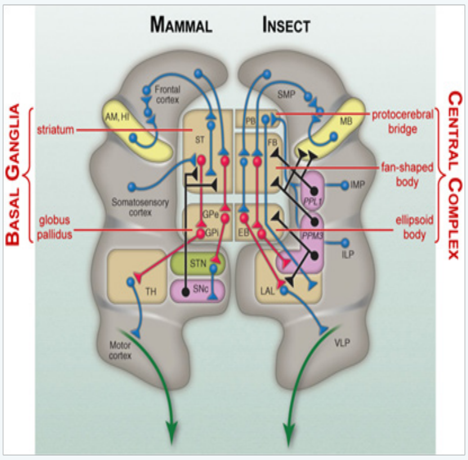

Figure 4. Comparison of the mammalian brain and the insect brain [Strausfeld & Hirth 21].

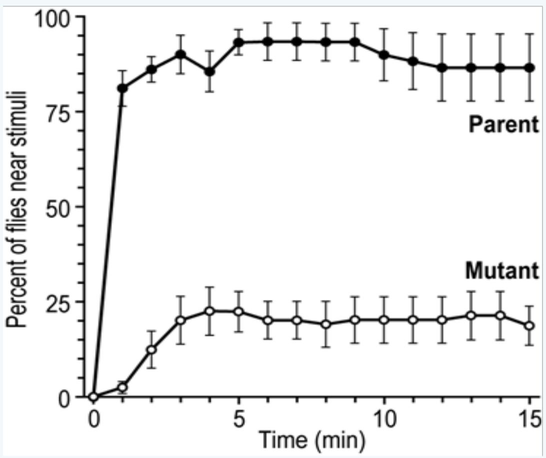

Figure 5. Parental *Drosophila* are attracted by many stimuli ("parent") and repelled by many other stimuli (not shown here). Motile mutants were isolated that fail to be attracted by any of these ("mutant") and fail to be repelled by many other stimuli (not shown here) Vang & Adler [24].

Decision making, a function of the prefrontal cortex in people and other primates, has been found in *Drosophila*, too According to Alder. The flies at one end of a tube largely refused to go to the other end containing attractant together with overpowering repellent, but mutants could be isolated which did go there. These mutants presumably had a defect in deciding what to do.

Analogous to the prefrontal cortex in humans and other primates, the central complex of the fly is presumed to be in control of behavior. Some thirty *Drosophila* mutants defective in the fly's central complex have been isolated by Richard Strauss & Martin Heisenberg [26], Kirsa Neuser et al. [27], Joanna Young & Douglas Armstrong [28], and others. We found that three of these are defective in bringing about behavioral responses Vang & Adler [24]. Using them, one can learn how the central complex generates a behavioral response.

Working memory, a part of the prefrontal cortex first described in people and other primates, has now been found in insects, too. This was discovered by Roland Strauss et al. [27], who showed that *Drosophila* can remember the position of an object for several seconds after the object has been removed, as illustrated in (Figure 6). By using mutants, the authors [27] found that this behavior depends on ring neurons of the ellipsoid body in the brain's central complex.

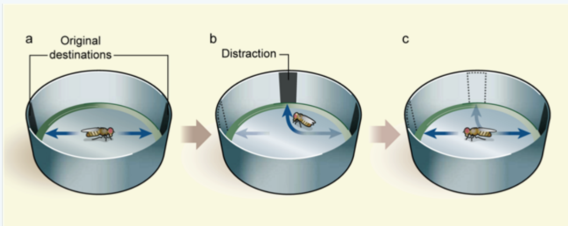

Figure 6. Seth Tomchik & Ronald Davis [162] have described the Neuser et al. [23] experiment in this way: A) A fly will walk back and forth between two opposing black stripes in a circular arena. B) Then midway it is distracted by a new black stripe to its side.C) When the distracter stripe subsequently disappears, the fly resumes walking along its original course even though it no longer sees the original destinations.

Charles Darwin's study of the behavior and intelligence of earthworms is presented in his 1881 book, "*The Formation of Vegetable Mould, through the Action of Worms with Observations on Their Habits*." [35] Earthworms plug the openings of their burrows with leaves. Darwin did experiments to study the worm's reactions to variation in the shape of the leaves, for example he used cut leaves, pine needles, and "leaves" made from paper. He showed that the worm feels the shape of the leaves prior to grasping them and that it used judgment about the best way to pull the leaves into their burrow. Darwin said: "If worms have the power of acquiring some notions, however crude, of the shape of an object and of their burrows as seems to be the case, they deserve to be called intelligent; for they act in nearly the same manner as would a man under similar circumstances... One alternative alone is left, namely that worms, although standing low in the scale of organization, possess some degree of intelligence; this will strike every man as very improbable, but it will be doubted whether we know enough about the nervous system of the lower animals to justify our natural distrust of such a conclusion".

What is in Charge of the Behavior of a Plant?

Evidence for The Boss and executive control in plants has not been presented, but it could be implied by some of the following work.

Studies by Charles Darwin and his son Francis on the behavior of plants, reported in 1881 in their book, "*The Power of Movement in Plants*", [36] led them to conclude, "Finally, it is impossible not to be struck with the resemblance between the forgoing movements of plants and many of the actions performed unconsciously by the lower animals ... Yet plants do not of course possess nerves or a central nervous system; and we may infer that as with animals such structures serve only for the more perfect transmission of impressions and for the more complete intercommunication of the several parts...We believe that there is no structure in plants more wonderful as far as its functions are concerned than the tip of the radicle [the root] ... It is hardly an exaggeration to say that the tip of the radical thus endowed, and having the power of directing the movements of the adjoining parts, acts like the brain of the lower animals".

The plant physiologist Wilhelm Pfeffer statedinhis1897 book "*The Physiology of Plants*" [37]:"the fact that in large plants the power of growth and movement are not strikingly evident has caused plants to be popularly regarded as 'still life'. Hence the rapid movements of sensitive *Mimosa pudica* were regarded as extraordinary for a plant… If mankind from youth upwards were accustomed to view nature under a magnification of 100 to 1000 times, or to perceive the activity of weeks or months performed in a minute, as is possible with the aid of a kinematograph, this erroneous side a would been tirely dispelled". Pfeffer studied the "behavior" of plants, both rapid catching of insects and also slow growth-responses to environmental stimuli, called tropisms.

Jagadish Chandra Bose was first a physicist, working on electromagnetic radiation, then he spent thirty years studying electrical signaling in plants. His major conclusion, presented in "*The Nervous Mechanisms of Plants*" in 1926 [38]: "Ordinary plants, meaning those usually regarded as insensitive, exhibit the characteristic electric response already known in 'sensitive' plants. Ordinary plants were regarded at the time as in excitable, because they did not respond to stimulation by an obvious movement ... I was, however, able to show that every plant, and even each organ of every plant, is excitable and responds to stimulus by electric response of galvanotropic negativity ... The most important fact established in plant-response was the nervous character of the impulse transmitted to a distance. My discovery of the excitatory polar action of an electric current and its transmission to a distance, proved that the Conduction of excitation in the plant is fundamentally the same as that in the nerve of an animal".

Action potentials in plants have been extensively studied, see for example those of the Venus fly trap, the touch-sensitive *Mimosa*, and pea, as described by Clifford Slayman [39] and reported by Michael Sussman [40]. Thus action potentials occur in both carnivorous and non-carnivorous plants, but they are slower than those of the squid giant axon.

In "Plant neurobiology: an integrated view of plant signaling", Eric Breuner [41] reviewed the evidence that the behavior which plants exhibit is coordinated across the whole organism by some form of integrated signaling, communication, and response system. Studies of the neurobiology of plants have been stimulated by the creation of the Society for Plant Neurobiology; in its 2006 symposium book, "*Communication in Plants: Neuronal Aspects of Plant Life*", František Baluška et al. and Peter Barlow say [42], "Roots represent the essential part of the plant whereas shoots can be dispensable…. Each root apex is proposed to harbour brain-like units of the nervous system of plants. All 'brain units' are interconnected via vascular strands (plant neurons) with their polarly-transported auxin (plant neurotransmitter), to form a neuronal system of plants". The Society in 2009 was renamed "The Society of Plant Signaling and Behavior" and its journal was renamed "Plant Signaling and Behavior."

Daniel Chamovitz [43] published "*What a Plant Knows, a Field Guide to the Senses*" to review a plant's equivalent of our senses: what a plantsees, smells, feels, etc. Asan example, Chamovitz reviews how the parasitic not-green dodder plant locates its prey: it grows toward a certain chemical given off by a green plant such as the tomato and away from another chemical given off by a different green plant such as wheat, according to Consuelo De Moraes et al. [44].But Chamovitz rejects the idea that plants are a subject for neurobiology.

What is in Charge of the Behavior of a Microorganism?

Evidence for The Boss and executive control in microorganisms has not been reported, but it could be implied in some of the following work.

The physiologist Max Verworn, who studied unicellular organisms and nerve cells, wrote in 1889 in his book, "*Psycho-Physiologische Protisten-Studien*" [45] "My dear professor! When under your guidance I began my instruction in zoology, it was from the very beginning the life of the lowest organisms that interested me the most. For here, on the lowest level of life, within the framework of one single cell, all the phenomena of life which we observe in the higher organisms can be found in their most simple form. Tobe sure some physiologists do not yet recognize psychology as part of physiology; yet if physiology considers the investigation of the phenomena of life to be its task, then the consequences of this conception is obvious, for the psychic processes are just as well phenomena of all life as are the metabolism processes." Eukaryotic microorganisms and bacteria were included in Verworn's studies

The behavior of microorganisms was reviewed by Alfred Binet, the father of the IQ test, in his book "*The Psychic Life of Micro-organisms, a Study in Experimental Psychology*" [46]: "I have endeavored in the following essay upon micro-organisms to show that psychological phenomena begin among the very lowest classes of beings; they are met with in every form of life, from the simplest cellule to the most complicated organism. It is they that are the essential phenomena of life, inherent in all protoplasm... Thus, even on the lowest rounds of the ladder of life, psychic manifestations are very much more complex than is usually believed". Eukaryotic micro organisms and bacteria were included in Binet'sreview.

Motile cells of animals have been studied: for example leukocytes, which are amoeboid cells of the immune system, by Martha Cathcart [47] and Connie Wongetal.[48]; and flagellated sperm interacting with egg, by Roy Caplan, Michael Eisenbach et al.[49].

The behavior of the protist *Physarum polycephalum* has been studied by William Dove and collaborators [Burland et al. 50]. Patterns of inheritance, its development, and its mitotic cycle were revealed.

In the yeast *Saccharomyces cerevisiae* two haploid cells of opposite mating type, a and @, fuse by a chemotropic response to their pheromomes [Cross, Hartwell et al. 51]. The mechanism of this fusion is being studied by use of mutants that fail here [Arkowitz 52; Gelin-Licht 53].

Discostelium discoideum are social amoebae whose behavior has been studied by Peter Devreotes and others [Swaney 54]. These cells depend on chemotaxis to find food and to survive starvation conditions. Their movement relies on the extension of pseudopods. Mutants missing various components have been isolated and studied.

The behavior of the ciliated protozoan *Paramecium* was placed on a mechanistic basis by the research of Herbert Jennings [55], Yutaka Naitoh & Roger Eckert [56], and Boris Martinac, Yoshiro Saimi & Ching Kung [57]. It was shown that the movement of *Paramecium* is regulated by electrical events caused by the flow of ions such as potassium and calcium, and that there is a genetic basis for this movement.

Theodor Engelmann discovered in 1881 that bacteria are attracted to light ("phototaxis") [58], and in the archaeon *Halobacterium salinarum* the role of microbial rhodopsin in phototaxis is now biochemically described by John Spudich [59]. Wilhelm Pfeffer [60] discovered that bacteria are attracted and repelled by various chemicals ("chemotaxis"), and in the bacterium *Escherichia coli* a biochemical mechanism for chemotaxis has been summarized[Adler 61; Hazelbauer 62]. Ann Stock and Igor Zhulin have called for a special issue of Journal of Bacteriology for reports on two-component signal transduction in bacteria and archaea (2017, in preparation). Gliding motility and multicellular swarming in the bacterium *Myxococcus xanthus* has been studied by Dale Kaiser [63] and by David Zusman [64].

How Behavior is Controlled

For organisms in general, the mechanism of behavior and the control of behavior are summarized in Figure 7. There are sensory inputs, both for external and internal stimuli. Then the organism chooses what to do about these by means of decision making. That result is then sent to the final pathway, which dictates a behavioral response. Decision making is directed by executive function which in turn is influenced by The Boss. Sam Gilbert and Paul Burgess [6] wrote "Executive functions are the high-level cognitive processes that facilitate new ways of behaving...The operation of executive processes accompanies a very wide range of behaviors." The idea that in *Drosophila* the control of decision making is made by executive function and The Boss was suggested by Lar Vang and Julius Adler [29]; see also Adler [61].

The interaction between stimuli and decision making (Figure 7) has been studied/reported by Marcus Raichle [65, 66], Dennis Bray [67], Björn Brembs [68] and Axel Gorostiza, Julien Colomb & Björn Brembs [69]. There is an active state that is present before stimuli are presented, then a different state upon presentation of stimuli. Although discovered in mammals by Raichle [65, 66], such a phenomenon occurs also in invertebrates as described by Dennis Bray [67]. A decision-makingprocess has been reported by Alex Gorostiza, Julien Colomb & Björn Brembs [69].

Here are examples of decision making in the case of attractant together with repellent: in people, Grabenhorst et al. [15], Rolls et al. [16] (see Figure 2); dogs, Andersson et al. [70]; insects, Dethier [71], Tang & Guo [72], Zhang et al.[73], Yang et al. [74], Joseph et al. [75], Vang et al. [76], Adler & Vang [30]; worms, Ishihara et al. [77]; plants, Liscum & Briggs[78], Hangarter [79]; and bacteria, Tsang et al. [80], Adler & Tso [81], Schultz et al. [82]. These can be viewed as valuable for trying to find out if a study of conflicting behavior might yield information about executive function.

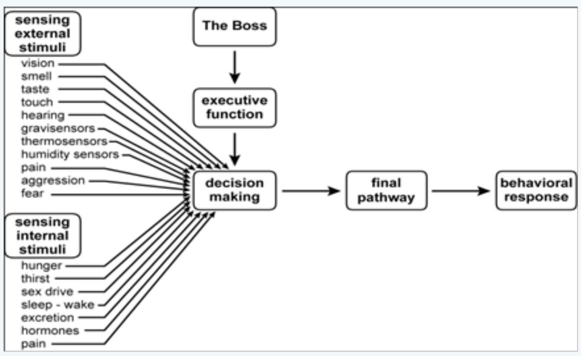

Figure 7. Where decision making, final pathway, and behavioral response are thought to act in organisms in general. Control of decision making by executive function and The Boss is indicated. The interaction between stimuli and decision making is complex, see text. Final pathway in the case of animals involves the central complex (Figure 3) or frontal cortex/basal ganglia (Figure 4).

Especially valuable will be those cases above where it has been possible to isolate mutants that could involve a defect in decision making or in executive function and perhaps even in The Boss":

Tang & Guo [72], Ishihara et al. [77], Vang et al. [76], Zhang et al. [73], Yang et al. [74], Joseph et al. [75], Adler & Vang [30].

When there is a change in environment or a change internally, The Boss determines what is needed to compensate, and then executive function carries this out by way of decision making (Figure 7). For example, a bad taste may prevent an organism from consuming a needed substance, but if the organism is starved for that substance The Boss can change the system so that the valuable substance is anyway consumed. How that is achieved is presently unknown.

An example of change is shown in Figure 8, where a *Drosophila* mutant changed its property over a 20 day period. As it aged, the response changed: the mutant became attracted to attractant plus overpowering repellent where previously it was repelled [Adler & Vang 30]. What is the mechanism for such a change? That needs to be discovered. In people, Altzheimer's disease is such an age-dependent behavioral change that needs to be understood [Selkoe et al. 83].

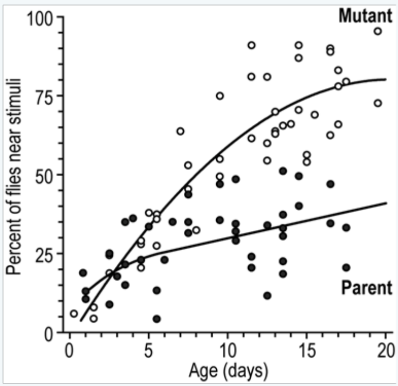

Figure 8. Parental *Drosophila* largely stayed away from a mixture of attractive light plus overpowering chemical repellent ("parent"). Mutants were isolated that did not stay away when the flies got older ("mutant") although they remained attracted to light alone and repelled by chemical repellent alone Adler & Vang [25]

Metabolism and its Control

At first scientists learned about small molecules (for example glucose) and then about enzymes, then it became known that there are genes that made the enzymes, and now mechanisms are known that control the genes. Initially specific controls were discovered, like the operon that is in charge of the metabolism of lactose [Jacob & Monod 84, Beckwith 85]. Then it was found that related operons could be controlled by a common regulator, the regulon [Neidhardt 86, Beckwith 85], [Neidhardt & Savageau 87]. Sets of operons are coordinately controlled by global regulators, as described by Susan Gottesman [88]. The global regulators of *E. coli* evidentby2003 have been reviewed by Augustino Martinez-Antonio & Julio Collado-Vides [89], see their figure reproduced here (Figure 9), which tells that there are seven global regulators that are sufficient for modulating the expression of 51% of the genes in *E. coli*. Thus a few global regulators have a large influence.

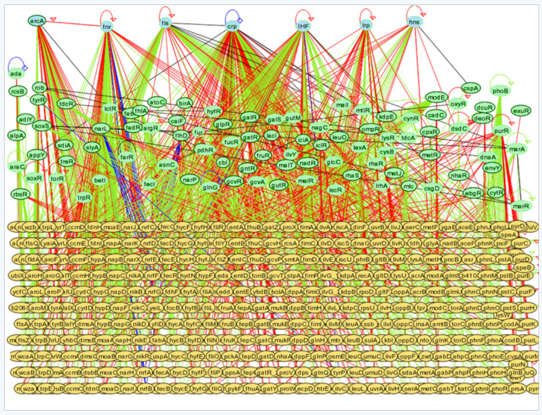

Figure 9. Overview of the transcriptional regulatory network in *E. coli* according to Martinez-Antonio & Collado-Vides [83]. Regulated genes are shown as yellow ovals, transcription factors as green ovals, and those transcription factors considered to be global regulators as blue ovals (the blue are arcA, fnr, fis, crp, IHF, lrp, and hns). The green lines indicate activation, red lines indicate repression, and dark blue lines indicate dual regulation (activation and repression). As an example, Crp (see crp in the figure) is a master regulatory protein which controls 197 genes by means of sensing the energetic status of the cell according to the level of cAMP, and this in turn controls, among other things, the synthesis of flagella and of the chemotaxis system.

CsrA is a bacterial global regulator. Tony Romeo et al.

[90] showed that CsrA, an RNA binding protein, can interact with RNAs of at least 721 genes. Some of these RNAs function positively to make the enzymes needed for the growth phase and some function negatively for inhibition of these enzymes in the approach to stationary phase.

Some further examples of global regulatory pathways follow. In the case of response to stress, *E.coli* represses its housekeeping genes and turns on genes for handling noxious conditions such as heat, a high salt concentration, radiation by ultraviolet light, acidic pH, and ethanol according to Tanja Gruber & Carol Gross[91]. It does this by replacing the sigma factor for turning on housekeeping genes with sigma factors for turning on genes that mediate the emergency, thus regulating 225 genes – 203 positively and 22 negatively according to Tao Dong & Herb Shellhorn [92]. Similarly, upon exposure to heat, hydrogen peroxide, or a high salt concentration, yeast represses about 600 genes related to synthesis of normally required proteins and induces about 300 other genes needed for the stress response, according to Audrey Gasch et al. [93].This occurs partially through changes in chromatin brought about by means of deacetylation of histones in both coding and non-coding regions.

In a systems biology approach, Andrew Joyce & Bernhard Palsson [94] have shown that one can interpret genomic results to indicate that certain components are global regulators and others are genes for enzymes that are targets. They illustrate 104 regulators of E.coli that control 479 genes for target enzymes. Covert et al. [95] say, "We expect that after an effort of some years and many iterations of this process, regulatory network elucidation for *E.coli* will be essentially complete."At that time one will be able to tell which components control all the rest.

Development and its Control

In the case of development, the *hox* genes of an embryo act to regulate genes that in turn regulate large networks of other genes; for example in *Drosophila* the *hox* genes regulate the genes that form the organs of each segment, including the genes that form appendages, according to William McGinnis and collaborators[Pearsonetal.96].

Also in development, there is a general transcription factor, Lola, that regulates axon path finding in the *Drosophila* embryo. Edward Giniger, Liqun Leo, and collaborators have shown that the *lola* gene controls some of the earliest steps of development as well as later stages [Spletter et al. 97]. This gene, which by alternative splicing makes 20 isoforms, regulates the expression of at least 1,000 to 1,500 other genes [Gates 98]; unpublished data of Edward Giniger. Thus lola was called a "master regulator" by Giniger and coworkers: it orchestrates the appropriate expression of guiding factors, receptors, and signaling proteins that execute the guidance decisions of a given growth cone [Madden et al. 99]. The involvement of RNA in development has been studied by Scott Aoki et al.[100].

Immunological Response and its Control

In the case of immunological responses, it is the synthesis of lymphocytes from stem cells that is globally regulated. This regulator is Early B-cell Factor acting by way of Pax5, which is a transcription factor that activates 170 appropriate genes and represses 110 inappropriate genes, as documented by Cesar Cobaleda et al. [101] and KaraLukin et al. [102]. This action results in commitment to making the lymphocytes.

Reproduction and its Control

Mating in bacteria ("conjugation") is the transfer of genetic material from a "male" into a "female" bacterium. This was discovered by Joshua Lederberg & Edward Tatum [103] and has been further studied to the present time [Gomis-Ruth et al. 104]. In animals sex steroids are crucial for reproduction [Guerriero 105]. In plants Sun et al. [106] a in bacteria Bode et al. [107] demonstrated that such steroids also occur but any function in reproduction is not yet determined.

For reviews see Graham Bell [108] *The Masterpiece of Nature: The Evolution and Genetics of Sexuality; Richard Michod* & Bruce Levin [109] *The Evolution of Sex: an Examination of Current Ideas*; *Sarah* Otto and Thomas Lenormand [110] *Evolution of sex*: *Resolving the paradox of sex and recombination*.

THE BOSS

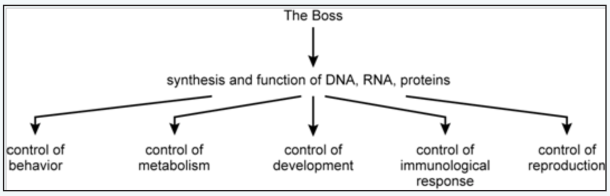

Figure 10. Summary of the role of The Boss.

Behavior, metabolism, development, immunological responses, and reproduction, each discussed above, are controlled by The Boss. There is one Boss for all these functions. The Boss is perhaps the same for all organisms. What is The Boss and how does it control? The Boss is an unknown hypothetical mechanism that directs the synthesis and activity of DNA, RNA, and proteins and thereby is in charge of behavior, metabolism, development, immunological responses, and reproduction (Figure 10).

Essential Genes and The Boss

Now that we know the sequence of deoxy nucleotides in the DNA of many different organisms (humans, rats, mice, fish, flies, worms, yeast, plants, bacteria, etc.), one can try to find out, for each organism, which are essential genes. Non-essential and essential genes are defined in the following way: Elimination of a non-essential gene (by mutation) still allows the organism to survive, while elimination of an essential gene (by mutation) leads to death. Essential genes are shown in (Figure 11). There are essential genes whose functions are still not fully known. Their functions need to be determined. And what, if anything, controls the various essential genes, what turns them on and off? That itself may be The Boss (Figure11).

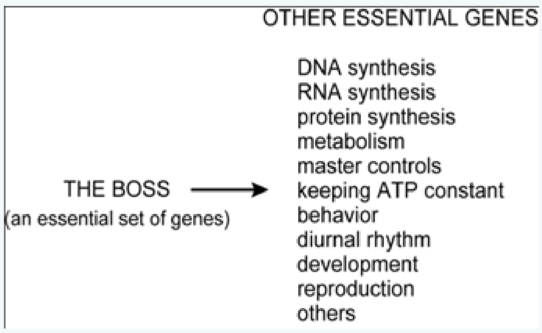

Figure 11. Essential genes and the role of The Boss. Various essential genes may be controlled by The Boss, which is itself a set of essential genes. Genes believed to be essential are listed here. These include genes for DNA synthesis, RNA synthesis, protein synthesis, and metabolism (in the case of *E. coli* see Baba et al. [105]. Some of the processes listed diurnal rhythm. The role of ATP is discussed by [Vang & Alder 106] Greer et al. [107].

How many essential genes are there? The list of essential genes has not yet been completed in humans [total number of genes 20,000-25,000] [International Human Genome Sequencing Consortium114], in mice [total20,00-25,000][Mouse Genome Sequencing Consortium 115], in zebra fish [total about 25,000] [Herrero et al. 116], and in *Arabidopsis* [total about 26,000] [*Arabidopsis* Genome Initiative 117], butin *Drosophila* there are about 3,700 essential genes out of atotal of 13,379 genes [Adams 118], in *C. elegans* about 5,700out of 19,427 [*C. elegans* sequencing consortium 119], in *Saccharomyces cerevisiae* 1,105 out of 5,916 [Giaever et al. 120], in *E. coli* 303 out of 4,377 [Baba et al. 111], in *Mycoplasma genitalium* 382 out of 482 [Glass et al. 121].

The fact that *E. coli* has so few essential genes (303 of them), compared to a much larger number in eukaryotes, makes the search for The Boss seemingly easier in *E. coli*. Finding out how The Boss might control those essential genes is one way for identifying The Boss.

Synthesis of DNA, RNA, and Protein in Relation to the Boss

Our knowledge of how DNA, RNA, and proteins are made, and how this is controlled, is now extensive for DNA synthesis [Kaguni 122, Zakrzewska-Czerwinska et al. 123, Katayama et al. 124, Masai et al. 125]; for RNA synthesis including the spliceosome [Wahl et al. 126, Jackson et al. 127, Malys & Mc Carthy128,Nakagawaetal.129,Hoskins&Moore130; and for protein synthesis [Thomas & Chiang 131, Passalacqua et al. 132, Jiang & Pugh 133, Sorek & Cossart 134]. As an example, there is a time during the cell cycle when DNA synthesis is turned on and a time when it is turned off. The proposal here is that there is a master control, The Boss, that dictates what shall be the state of synthesis of DNA, RNA, and proteins.

A remarkable discovery, made by Zachary Burton, Carol Gross, Richard Burgess et al. [135] and by James Lupski, Bob Smiley & Nigel Godson [136], is the existence of an operon in *E. coli* that directs all three of the most essential components of anorganism: DNA (dnaG, which makes DNA primase), RNA (*rpoD*, which makes a part of RNA polymerase), and protein (*rpsU*, which makes a part of ribosomes). See Fig. 1 of Lupski and Godson [137] for a summary. How is this *dnaG-rpoD-rpsU* operon, also known as macromolecular synthesis operon, turned on and off? It seems possible that The Boss may control the operon.

DNA other than Protein-Coding Genes

Bacteria and eukaryotes have very roughly a similar number of genes that code for proteins (400 to 5,000 for bacteria and about 6,000 to 25,000 for eukaryotes) but in bacteria most of the DNA is genes that code for proteins while in eukaryotes the DNA-coding genesare only a small part of the DNA. For example, in mammals it is only1-2% [Mercer et al. 138], see (Figure12).

The amount of DNA/cell in bacteria is about 3-4 million base pairs/cell, about 12 million in yeast, about 180 million in flies, and about 3 billion in humans, in accord with approximate complexity (although some amphibians have 25 times as much DNA as human cells)[Moore139,Darnell140].

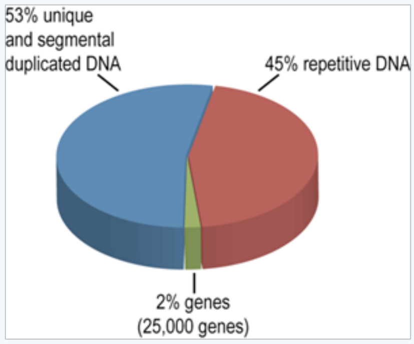

Figure 12: Only a small part of the DNA is genes, about 2% in humans. As to the rest of the DNA, unique sequences are found just once; segmental duplications are chunks of DNA found multiple times; repetitive sequences include different classes of repeats such as LINEs and SINEs. All this, including the figure, comes from Zhang et al. [64], who based this on figure 1 published by Andrew Shedlock [65].

Recently workers have shown that 70 to 90 percent of the eukaryotic DNA produces RNAs which do not make proteins and don't end up being ribosomal RNA, transfer RNA, or known controlRNA[Merceretal.138,Nagalakshmietal.141,Wanget al. 142, Ozsolak et al. 143].Some of such RNAs occur also in prokaryotes [Sorek & Cossart 134, Siezen et al. 144] Thus a large part of the DNA in eukaryotes makes RNAs that control the organism in unknown ways. How such RNAs function is currently being investigated, both in eukaryotes [Wang et al. 142, Ozsolak et al. 143] and in prokaryotes [Sorek & Cossart [134], Siezen et al. [144]. These studies all point to non-coding RNA as a source of regulatory elements [Carninci & Hayashizaki 145].

Thus the biological complexity of organisms is not reflected merely by the number of protein-making genes but by the number of other physiologically relevant interactions, say Michael Stumpf et al. [146]. The whole set of molecular interactions in cells has now become known as the "interactome"; this includes protein-DNA interactions, protein-RNA interactions, and protein-protein interactions, according to Sanchez et al. [147]. Such interaction maps have been presented for *Drosophila* by Sanchez et al. [147] and by Giot et al. [148]. The size of interactomes correlates much better with their apparent biological complexity than does the size of the genome; thus the number of interactions in humans is estimated to be about 650,000 compared to about 25,000 genes in the human genome, say Stumpf et al. [146].While much progress has been made in describing interactomes, we are still far away from completion because the interactome considers the whole organism and thus there is the need to collect a massive amount of information.

A novel method for studying regulators of transcription is chromatin immune precipitation (ChIP, also ChIP-chip) studied by Mooney et al.[149]. By this method, formation of acomplex between DNA and proteins can now be studied on a global scale by isolating the complexed part, precipitating it with antibody to the protein, then identifying the DNA portion. This method has been successfully used in humans, other animals, yeast and bacteria. The results tell that certain parts of the DNA interact with transcription factors and with sigma factors that allow RNA synthesis to take place. In short, the regulatory parts of the DNA are being identified by this method. A different method focuses on the interplay between transcription factors and micro RNAs, studied by what is called the "yeast one-hybrid (Y1H)" method; this work is also being widely pursued and especially by Marian Walhout's group in *C.elegans* [Martinez&Walhout150].

OK, there are regulators in charge of many functions. Do the regulators act independently of each other, or is there something that controls them? It seems that independent function of each regulator would result in competition and confusion incompatible with the life of the organism. Something must be coordinating them. It is The Boss. But that is only an idea at this time.

Chemistry of the Boss

What is The Boss? Of course it must be a gene or genes and it must be essential (Figure 11). The gene(s) for The Boss would seem to be made of DNA, but not necessarily since RNA may have been present in organisms before there was any DNA, according to ideas of Carl Woese [151], David Baltimore [152], Walter Gilbert [153], and Raymond F, Gesteland & John F. Atkins [154] Gerald Joyce [155], Jennifer Doudna &Thomas Cech [156]. Since The Boss may already have occurred in these earliest organisms, The Boss genes might well be RNA that does not go through any DNA at all, like many of the known RNA viruses [Woese151].

Initially The Boss may have been a phospholipid that controlled RNA in the absence of DNA and protein. There as on for suggesting this is that phospholipids probably were present in those initial membranes [Coleman157, Milan158]. Alkaline phosphatase was likely present and its level could be controlled [Torriani 159].The interaction of phospholipids with RNA has been documented [Yarus et al. 160-162]. Such interaction at the start could have been the beginning of the Boss.

To identify the Boss

As described above, behavioral mutants that could possibly be defective in executive function and perhaps even in The Boss may have been isolated. The control of any essential gene by The Boss (Figure 11) could be studied by obtaining mutants that fail there. In addition, reverse genetics will be useful to dissect these biological processes by inhibiting gene-expression [Snustad&Simmons163].

Summary

a. The behavior of various organisms – people and other primates, "simpler" animals, plants, microorganisms – has been reviewed and its direction by executive function and The Boss has been suggested.

b. The role of global regulators directing metabolism has been reviewed.

c. The role of master regulators directing development has been discussed.

d. The control of immunological response has been discussed.

e. The control of reproduction has been discussed.

f. The idea that each organism is under control by The Boss has been presented. It is proposed that The Boss is in charge of the organism by way of controlling behavior, metabolism, development, immune response, and reproduction, as shown in (Figure10).

g. Synthesis of DNA, RNA, and proteins has been discussed in relation to The Boss (Figure10).

h. Essential genes have been discussed in relation to

finding The Boss (Figure 11).

i. DNA other than that which codes for synthesis of proteins has been discussed in relation to The Boss (Figure 12).

j. As to the chemistry of The Boss, this is unknown. It could be DNA, or it could be RNA that functions independently of DNA.

k. Studies of the Boss and of control of behavior, metabolism, development, immune response, and reproduction will be carried out further.

Alternative Views

The Boss is a hypothetical entity; there is little or no evidence for it at this time.

An alternative is that there is no central boss at all but instead there is a special boss for each of the five parts. Another alternative is that it doesn't require any boss at all to get interaction between behavior, metabolism, development, immune response, and reproduction. Each of these may interact with each other but without any control by a boss. So it is possible that there is no boss. There is no evidence to support any of these above alternatives at this time. It will require further research to determine which of these ideas (if any) is correct.

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