KNOWLEDGE OF BRAIN MEMORY CODIFICATION AS A CHALLENGE FOR THE THIRD MILLENNIUM

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This contribution proposes to trace the pathways of receiving, accumulating and reading the information coming from the external world. The intriguing subject is dealing mainly with suggestions in the realm of common knowledge in Biophysics, Physiology and Molecular Biology. Even though these suggestions have not yet been fully supported by experimental data, the reasoning seems to hold up with a certain logic and can be used as a basis for a long-term program of researches concerning the old but always new open problem of brain memory.

Working on changes in the genetic code as evoked randomly by natural factors, selection has conditioned the development of living matter. All reproducing creatures, from virus to man, are capable of storing in their hereditary patrimony certain genetic information. This can be called a primary memory which within wide limits is manifested in the various species. Its principle is general. It is resolved in the specific sequence of the elements which compose the gene program (1). Each structural element must necessarily be formed in the cells in accordance with this program, while its significance continues from generation to generation unchanged for as long as the genetic information does not change (2). Nevertheless, there is "news" in this general theory of information - news which becomes evident when one goes on to study, for example, the neuron-glial molecular interactions (3-6). The birth of nerve cells

represented a new event in the development of living matter which thereafter became capable of storing even the most fleeting items of information coming from the exterior. In other words, although genetic memory is located in all tissues, from sperm to epidermis, and in the brain itself, there exists another type of memory which can be stored in the nerve cells only (7). We are dealing here with a more specific memory not so wide in range, and maximally limited to the life of the individual (8). If the genetic program could be called a primary memory and its language a primary code, we could call the memory of the nerve cells a secondary or nervous memory and its language a secondary code.

Is it premature to think that research today may be able to discern details of the two codifying systems and correlations between them (9-11)? In fact, we can say that of the two systems the first - the genetic one - is relatively stable and develops according to endogeneous laws, since it maintains its equilibrium independently of the environment, while the other system - the nervous one - appears to be completely labile and conditioned by experience. That is, while the first memory does not completely reflect the external world, the second reflects nothing but the external world. Although an ordinary cell can conserve only the hereditary information which is inscribed in the DNA of the species, the nerve cell, in addition, can record the events of the exterior and remember them during its life.

We can ask to what extent the two systems may be based on a single principle and what are their specific molecular mechanisms?

When the question is put in this way, various problematic details arise. As we shall see later, these seem to characterize the nervous code as a form of highly organized living matter. At the same time, these may pose a formal parallel between the nervous code and the genetic code, since in both cases the storing of information may take place in a system, while the principle of the code language has to be none other than the specific arrangement of small structural elements in the body of this system. In the case of genetic information, this has been demonstrated (12-15). In the case of nervous information, it remains to be shown whether a chemical

system is involved and, if so, what kind - biopolymers like proteins and glycoproteins or some other complicated macromolecular or super-macromolecular structures like membranes. But this indeed is a detail which does not impede the discussion of the problem. The important point is to establish a formal parallelism between the genetic and the nervous languages, first in the principle of the code, the sequence, and second in the kind of material involved, the structure which stores the information.

- What kind of code? -

Differences between the two systems can be seen in the type of code. By now it has been generally acknowledged that genetic information is transmitted exclusively by means of a chemical code, based on the sequence of nucleotide triplets. On examining the nervous code, however, we could foresee that it cannot be solely chemical, because of the speed with which information is stored and the kind of path it takes. This suggests that the nervous code is much more complex, since the correlations of the individual with the outer world are physical and chemical in nature, and are realized by way of the sense organs. Whatever the information from the outer world may be, it must pass via these organs before being stored in the specific system of the brain. Thus, the first mechanism for recording information must be extremely rapid and selective. Only those signals which are decipherable by the sense organs reach the brain, which is equivalent to saying that the emphasis is placed on the potential of the individual receptive system.

Since the storage of information does not need to take place at the level of the sense organs (which guarantee only the fidelity of its transmission), it seems correct to say that at this site the mechanism is prevalently physical. Without going into complicated details, let the reader remember some findings relative to visual analysis. When the imput is maximal, the information accumulated in 130,000,000 retinal receptors must be transmitted to a few neurons, with minimal loss, by means of 800,000 filaments of optic nerve. When the information passes from a large number

of elements to a smaller one, the losses can be held down only if the codifying net contains elements capable of integration, that is, elements functioning as memory messengers. It follows that the physical mechanism is adaptable not only to the rapidity of the operation but also to the series of electrophysiological happenings. A train of impulses is apparently sent along the afferent pathways in response to each stimulus by means of a physical code. Already at this point, there appears a marked difference from the chemical nature of the genetical processes.

One hypothesis is that, once arrived at the brain center, the impulses written in the physical code must probably be translated into a physico-chemical process, or even into a pure chemical process, in order to be conserved. Let us neglect for the present the problem of where this is done, in neurons or glia, synaptosomes or in some constituent of the cytoplasm specific to the neurons. The important point is that, in order to persist lastingly in the memory, information originating in the external world must be translated into chemical structures; that is, the physical code must be translated into a chemical code. Just as the physical code would reflect a memory messenger of brief duration, so the chemical code would reflect a permanent memory. For convenience, the physical code could be called afferent and the chemical static.

- Efficiency of the translation system -

The efficiency of the translation system becomes apparent as one notes the rapidity of formation of a storage ring (which may be a macromolecule or a circuit - a "ring" - of macromolecules, or conceivably a much more elementary structure). Thus, some events are remembered easily and others not, while the so-called visual memory differs from auditory memory. In some cases a single recording is enough to fix a certain event in the memory, whereas in other cases many identical signals are necessary. This signifies that in some cases a given ring is formed easily and in others it is not, and there is a certain difficulty in the cases in which the signal must be repeated in order to be translated. This difficulty could depend on the functional state of the translator, on the

complexity of the signal, or on the clarity of the afferent code. Taken together, these three parameters may represent the efficiency of the translation system, and the following queries, although they do not affect the essence of the theory, are pertinent: does the translator function in the same way during sleep and wakefulness, or when it is "overworked"? Are some signals easier to be translated than others? Is the afferent code always distinct, when it reaches the translator, or may it be garbled by irrelevant signals which must be carefully sorted out one by one? What is the background?

In any case, one can understand that the efficiency of the translator is conditioned by the phenotype. This is a very important point, since the same signals from the external world do not necessarily provoke the same processes in different individuals. And, equally, we do not know whether a specific afferent code may be physically necessary for each type of signal. It seems, therefore, that a given individuality may depend upon the efficiency of the translation system.

- The storage elements -

At present we do not know whether the afferent physical code is transformed into a specific sequence of elementary units in a certain ring, for instance, of amino acids, in a protein, or of sugars, in a polysaccharide. For this reason, it is difficult to sketch out hypotheses as to synthesis of the chemical structure (11). Whatever the case may be, it is likely that the translation process may be bound to the formation of catalytic compounds or enzymes. In the past, many authors thought that the more probable macromolecules for storing a memory could be proteins (16-18). To be sure, there is still controversy about some of the methods and techniques used in their investigations. No one directly tested the proposition that a protein represents the molecular engram which is the permanent memory trace. They merely stress the fact that protein metabolism is an important parameter of neuronal function. Thus, in order to prove that a given molecule may be regarded as a permanent memory trace, a more rigorous set of experimental criteria should be

necessary: (i) the molecule must undergo a change of state in response to the experience to be remembered; (ii) the changed state must persist as long as the memory can be demonstrated; (iii) the specific disruption of the changed state must result in consequent loss of memory.

Let us consider, as a speculative example, the possibility that a protein may be implicated in memory storage. In such a case, the biosynthesis of this protein must necessarily occur on the polyribosomes. Then, all the molecular mechanisms become much more complicated. The afferent code would have to be preliminarily transformed into a specific polynucleotide, i. e. into a "messenger" which should reach the ribosomes in order to be transformed, in turn, into a permanent protein memory, with a given "code". But where would we place the translator?

The difficulty in answering to this question justifies why we are inclined to consider as rather improbable the old hypothesis that the afferent code would be translated directly into a sequence of nucleotides and stored there (19,20). In such a case, one should also suppose that different polynucleotide polymerases are acting, case for case. Another fact that is equally improbable is that the signal for formation of these enzymes should not derive from DNA but rather from cytoplasmic mechanisms specific for neurons and capable of being set in motion by the translator of the afferent code. Or perhaps one should suppose that in the neurons there may be "pleiotropic" polymerases, already prefabricated, with secondary catalytic sites broadly sensitive to the indications of the translator. But, up to now, enzymes of this kind are unknown.

The earliest experimental investigations were naively tempted to prefer the hypothesis of the nucleotides on the ground that they function well for genetic code and therefore would likely be able to serve for the secondary code as well. This would be an indefensible simplification. Anyway, the important speculation is that nervous information may be stored by codification in a certain elemental substrate which possibly is not even a macromolecule, but perhaps a circuit of macromolecules or, at the other extreme, a small molecule or even a more elementary system.

- Translational model -

It would seem that a model for translation of the afferent code into a structure must of necessity be based on depolarization, insofar as it is understood at all. Indeed we know that the arrival of a signal generates on the external surface of the neuronal membrane, for example, a wave of depolarization and that as the external surface becomes negative the internal surface becomes positive. This phenomenon might be important in creating a stable structure of memory.

In this connection, two models might be a matter of speculation here, one having to do with a direct impulse transcription and the other with a mediated impulse transcription.

The first model (fig.1) suggests that a signal characterized by a given physical code causes on the surface of the neuronal membrane not the formation of a simple wave of depolarization but the formation of a design of negative charges surrounded by positive charges. Correspondingly, a design of positive charges (with an extention determined by the quality of the signal itself) is formed on the internal surface of the excited neuronal membrane. The design of positive charges, formed in response to the signal during the time Δt, serves in this case as a factor of specificity for attraction of structural elements A, B, C - probably bipolar - furnished by an hypothetical support T. With such a mechanism, a structure storing the information of the signal is built. Nextly, as a consequence of the movement of the external wave of depolarization, the positive charges of the internal membrane are dynamically replaced by the negative ones, while the elements A, B, C as a packet are sent back to storage sites M by the same re-established negative charges. This movement of the elements A, B, C occurs in the same fashion as it occurred before when the negative charges had been "recognized" by the positive charges (the amino acids, being amphoteric, could play the role of structural elements).

The second model (fig. 2) suggests that the transcription site is given again by a membranal depolarization on the exterior and by a corresponding positive-tending site internally. The alternative, in

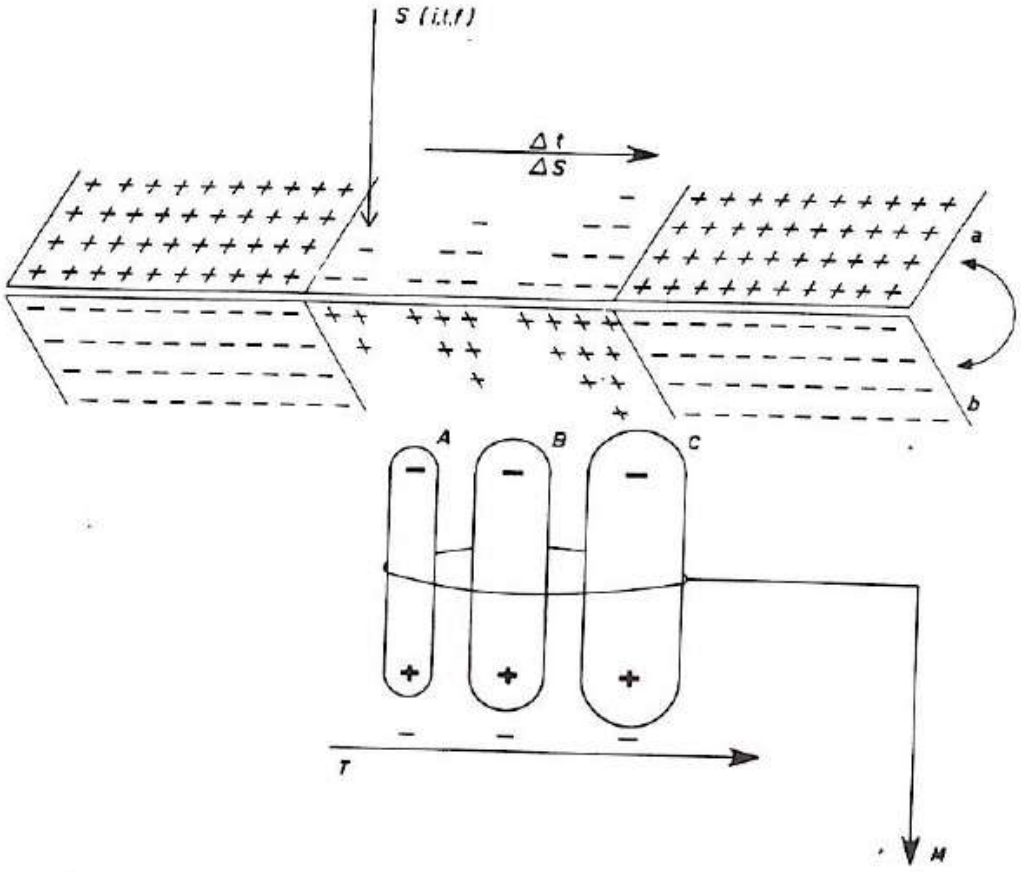

Fig. 1 - Translation model with a direct impulse transcription. A physical signal S with a code "itf" (i for intensity, t for duration and f for frequency) during the time Δt causes on the external surface a of the neuronal membrane the formation of a design ΔS of negative charges flanked by positive charges. Correspondingly, a design of positive charges is formed on the internal surface b of the excited neuronal membrane. This new design, made of positive charges, specifically attracts the elements A, B, C - probably bipolar - furnished by the negatively charged support T. M represents the system storing the information carried by the signal S.

respect to the first model, derives from the possibility that for transcription of the signal there are not many elements (recognized one by one by the submembranal charges), but instead there is a single macromolecular mediator endowed with a certain electrokinetic potential. This mediator assumes a spatial position depending upon the properties of the electropositive submembranal environment, so that from one time to another only a few of its active sites leaves a track on the hypothetical support T.

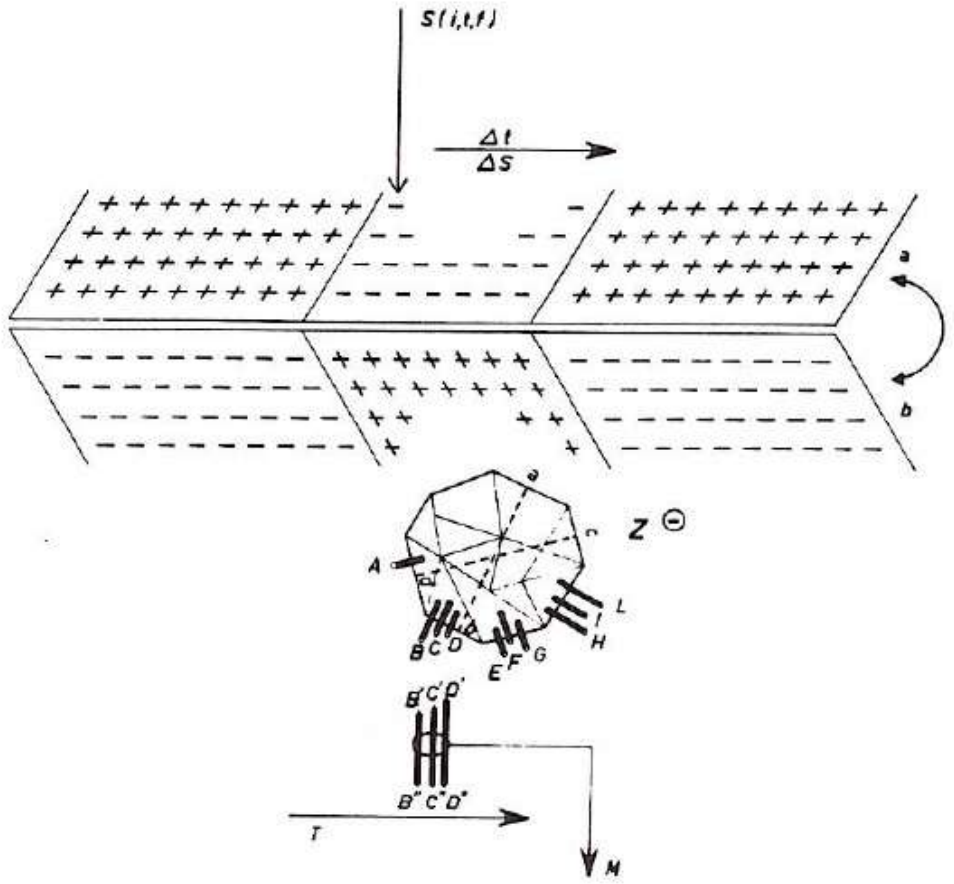

Fig. 2 - Translation model with a mediated impulse transcription. A physical signal S, with a code "itf" (i for intensity, t for duration and f for frequency), during the time Δt causes on the external surface a of the neuronal membrane the formation of a design ΔS of negative charges flanked by positive charges. Correspondingly, a design of positive charges is formed on the internal surface b of the excited neuronal membrane. This new design, made of positive charges, specifically attracts the macromolecular mediator endowed with a negative electrokinetic potential Z. While with an axis ab perpendicular to the plane of the support T its sites B, C and D leave a specific track on the same T, with an axis cd perpendicular to T the specific track is left by its active site A. Under other inclinations of the mediator, its sites E, F, G, H, I, L etc. can leave various specific tracks along T. As in figure 1, structural bundles of information can be formed and stored in the memory system M.

In other words, with an axis ab perpendicular to the plane of T, the sites B, C, and D leave a track, while with an axis cd perpendicular to T the track is left by the active site A. The role of mediator may be played by a protein-like macromolecule having on its surface a great number of radicals constituting the active centers A, B, C, D, etc. capable of

establishing specific bonds with elements A', B', C', D' etc. situated on T. As in the first model, structural bundles of information would be formed and stored (by means of a sole protein mediator it should be possible to transcribe an enormous quantity of information).

- The fate of the storage elements -

A theory of memory must not disregard one extremely important problem - that of the fate of the elements containing the engram. After translation, two alternatives are possible: either elements are conserved in a specific part of the nerve cell, waiting to be read at the right moment, or the molecule may begin to replicate uninterruptedly. Neither of the two assumptions can be excluded a priori. Reasoning subjectively, by anthropomorphic logic, one might argue that natural selection could not choose the alternative of continual replication, which would not be sustainable from the point of view of energy expenditure and would also appear over-complicated. However, such reasoning would leave us to suppose that nerve cells contain "static warehouses" characterized by extreme metabolic inertness, which are capable of storing the elements that have been formed. The fact remains that neurons are the only cells which, once formed, do not reproduce, and this could be the condition for conservation of the "storage ring". The idea that there may be continual replication of elements is based only on the difficulty of imagining that, for example, a chemical combination can be conserved for years and years.

- With what reading mechanism? -

The storage of information has biological value only if it can be read. Gene information is read by its translation into a protein. Nervous information is essentially translated into a process involving movement - either into an action or into a thought whose purpose is to express a reaction to a stimulus coming from the external world. Thus, the mechanism for reading the nervous engram cannot be analogous to that which permits the reading of purine and pyrimidine base sequences of nucleic acids.

At first glance, this problem appears too intriguing to state, even from a solely speculative point of view. Nevertheless, some aspects can be roughed out. The rapidity of the reading and the multiplicity of recorded events, which must be read simultaneously, make one think that the mechanism for reading the nervous engram must be predominantly physical. This conclusion is substantiated by the fact that, in the output as in the input, the information must rapidly pass rather long routes to reach the effectors. It follows that, once we have assumed the physical nature of the reading mechanism, we must also allow the existence of a second translator in the nerve cell, capable of reversing the sequence of structural elements into a new physical or efferent code.

Two considerations arise. (i) Is it possible that the translation from chemical to physical languages may be effected by the same translator whose work is to transform the afferent code into an engram? If so, what could be the mechanism of reversion? (ii) The possibility of a unique translator seems unlikely for the following reason. Whereas one might consider a single translator if the content of the afferent code were symmetrical, like a mirror image, this is not necessarily the case. Indeed almost certainly the efferent code must differ in content from the afferent code since the reading of the engram serves to bring about an action. In the latter case, it might be supposed that instead of a secondary translator a centrally integrated system exists, capable of using memory for relating. This system might be capable of reading the engram, integrating the information, and elaborating the efferent code in a creative way.

Let us examine two manifestations of the "integration system": the elaboration of a thought and a simple movement.

In the first event, the stimulus which is to set in motion the integration mechanism derives from the same brain. Thus, a thought may be the derivative of a central integrative process which is already operating because it, in turn, has been set in motion by an afferent stimulus. This interpretation led to believe that a thought can be the fruit of an endogeneous force completely independent of the environment. However,

on the basis of the schemes discussed above (figs. 1 and 2), it is obvious that whatever the central integration process may be - direct or indirect - it is always evoked by an exogeneous stimulus. The integration of the engram may happen in a quite intriguing manner during sleep. In this state, dreams are produced which once they have become events can be newly recorded in the memory. That is, two facts of extreme importance are in play: on the one hand, one must conclude that, if dreams are re-elaboration of a certain kind of engram, then it must be true that during sleep the central integration system can function in some manner; on the other, if we remember dreams, it follows that during sleep the systems for storing information also remain active. From this we arrive at the conclusion that sleep represents a functional phase of cerebral activity which is independent from the brain's basic activity - that of accumulating information from the external world. The remembering of dreams can serve as a basis for discussion of our complex psychic activity. Every time the integration system releases something new, this something can be recorded. A second-order memory is formed, from which a signal may be sent for another integration process which in its turn may well give rise to something which will be transcribed in an engram. It is obvious that from memories of second, third, fourth orders etc, derives the individual capacity to express thoughts, to store information, and hence to imagine - that is, to elaborate creatively.

The second event regards the routine movements themselves. Probably not all reflexes, which lead to movements, can be recorded in the form of engrams, and in any case this would be extremely wasteful. Some reflex movements should hence correspond to a reflex arc by means of which only physical codes may travel, avoiding storage. This idea is substantiated by the rapidity required for some reactions. Some obligatory movements may be simplified in the memory and written one single time for all uses.

- The relative independence of nervous memory -

A series of questions arises upon examining the problem of nervous

memory. (i) Does nervous memory, the secondary memory, depend on genetics or primary memory? (ii) Do organisms without a nervous system also have a secondary memory? (iii) Is nervous memory a tool of defense and survival of the individual and therefore of the species? (iv) Does it behave as a component of fitness? These questions have to do with the relative independence of the secondary memory. It is admissible that the process of accumulating information in the neurons may have inseparably accompanied the development of living matter. Just as the phenotype has conditioned the formation of certain engrams and has impeded others, so the nervous memory, in the struggle for life, has furthered the survival of some individuals. In this respect, memory has biological value as component of fitness.

Having stated the problem in this way, it would seem to be beyond doubt that the flexibility of secondary memory must depend upon the potential availability of a phenotype corresponding to a certain evolutionary level of genetic memory.

- Concluding remarks -

Many theories on the nature of brain memory have been advanced (21-25), some attempting to explain it on the basis of interneuronal exchanges (26,27), others on a more elemental basis that takes advantage of knowledge from Biophysics, Physiology and Molecular Biology (28-31). The first group of theories suggests that the accumulation of information in the brain is related solely to the closing of intercellular electric circuits (it considers the intricate anatomical organization of nervous tissue and the countless synaptic links); the second group of theories comprises those which trace analogy to the mechanism of antibody formation (32) and those which consider biopolymers as probable site of the engram (33). In such a framework, the available experimental information regarded particular details only as those showing that a decisive factor in memory processes is the ratio of catecholamines to serotonin (11). During learning some attention was paid, on the one hand, to the eventual increase of synthesis of given proteins and, on the other, either to the eventual

antibiotic inhibition of synthesis of these proteins or to their removal by sedimentation with specific antibodies through antiserum treatment (34). These two approaches did not show that a supposed specificity of given proteins is really needed for memory process. Since a protein may be requested for a number of events, it was claimed that in such kind of studies a background work has to exclude that this protein, being specific for learning, is needed for other processes too (35). Also, it was supposed that the proteins responsible for synaptic contacts and triggering impulses may participate as well in the creation of specific neuronal assemblies (36,37). A characteristic feature of brain is, in fact, that the information is perceived not by one of its single neurons but by a specific pattern of its neurons, while the association of nerve cells into a constellation capable of storing information depends on bioelectric impulses, chemical signals and axoplasmic transport. All this conformed with other neuron features, implying a bi-functional role of neurotransmitters: these are effective at the level of synapses and at that of subcellular structures (learning is facilitated by cyclic nucleotides via phosphorylation of specific protein-modulators). Although the actual sequence of chemical reactions underlying the synaptic transmission has to be studied, it was shown that the transmitters influence the life of neurons, for instance, the cationic transport ATPases. This appeared to be crucial in learning, since it was observed that both synaptic transmission and active transport are essential in the storage of memory. Of interest is the suggestion that a leading part in the realization of information encoded in a neuronal constellation is played by the so-called "biogenic amine transmitters", whose mechanism of action at the level of excitable membranes is one of the intriguing features in Neurobiology. Of no lesser interest is the information suggesting that the genetic apparatus may play a role in the process of neuronal memory (11). This role was associated with activation of gene coding for enzymes responsible for the critical level of neurotransmitters. Moreover, while the effect exerted by these substances was shown to deal with protein kinase stimulation by cyclic nucleotides, it was suggested that specific

neurotransmitters are involved in the reciprocal interactions between events proceeding at the level of synaptic membranes and events proceeding at the level of nerve cell nuclei.

Despite the fragmentation of these correlations with learning, essentially described during the 70's and the 80's, in the last twenty years the literature made efforts to distinguish several classes of biological memories - "genetic", "epigenetic", "immunological" and "neuronal". Since the genetic memory plays a leading role in all cell functions, it became of large interest to discuss how the work of the genetic apparatus may be associated with the process of neuronal memory. The first stage of memory was associated with the perception of external and internal stimuli, while the chemical reactions accompanying the perception of information were associated with a receptor cell (11). The efforts to investigate these phenomena at the experimental level remain, however, still far from a rational theory explaining the molecular basis of memory. The objective obstacles that neurobiological sciences have to overcome, before they can formulate a molecular theory of memory, are due mainly to difficulties of finding a proper model, because the organization of the brain is complex. It consists of many compartments having different functions associated with a multiplicity of biochemical reactions going in various directions and playing various roles in metabolism. For this reason, although knowledge of events concerning memory is still incomplete, one can attempt to begin an investigation at least on the events associated with the simplest form of memory, namely with the "conditional memory".

The present contribution did not intend to underestimate any one of the literature findings. Through a number of precepts it tried, nevertheless, to submit to the judgement of future investigators the peculiarities of a unifying view of the complicated process by which information may be accumulated in the brain. (i) The neurons, unlike all other kinds of cells, appear to possess double information: genetic information, inscribed in DNA, and information originating in environment. (ii) Information from the exterior may accumulate like a superstructure in the neurons and may

be conditioned by a specific genotype, so that its independence on the genetic code is only relative. (iii) If we admit that the process of accumulation of information is independent on the genetic code, it follows that its codification may be considered secondary to genetic codification. (iv) Having established priority and interdependence between the two codes, genetic and nervous, we outlined their analogies and differences. They are analogous because they can accumulate information in specific structures by arrangement of systemic constituents, and they are dissimilar because the nervous code substantially has physical components, input and output. (v) In contrast to the physical components of input and output, the gene expression steps (leading to biosynthesis of protein) must be considered as an essentially physico-chemical process. Then, it is reasonable to consider that the complicated nervous codification takes place by means of three steps: the first, physical, by afferent pathways; the second, physico-chemical, by conservation of information in a structure; the third, again physical, by efferent pathways. (vi) Among these three steps of the nervous codification arc, perhaps, there are two translators: the first engaged in changing the afferent physical code into the physico-chemical code of memory; the second in re-translating the language of memory into the efferent physical code. (vii) Given the "asymmetry" of the physical components of the circuit, it is logical to expect the two translators being quite distinct. The first must set up a structure, while the second must provoke a movement. The afferent and efferent coding systems, therefore, show evident differences. (viii) Finally, the static component of nervous codification would have to express itself in construction of a sequence of elemental units of greater or lesser durability.

But what should one foresee about the feasibility of elucidation of all these points? The XIXth Century led famous biologists to enunciate the theory of evolution, the theory of cell and the genetic laws. In the XXth Century, in addition to studies on biocatalysis and basic metabolic pathways, a large number of discoveries concerned the structure of the DNA double helix, the genetic code, the inverse transcription, the restriction enzymes, the

recombinant macromolecules. The same XXth Century provided information on the organization of the operon in bacteria, on the structure of the gene in eukaryotes, on the genetic regulation of transcription, on the post-synthetic modification of macromolecules, on the cell-virus interactions and on the gene sequencing. Despite this progress, three fundamental problems remain open. The first concerns the cell differentiation and its code. The second concerns the cancer de-differentiation. The third regards the intriguing differentiation of the neuron. Well, with the appearance of this cell type, there emerged for the first time in living matter the ability to record codified information originating not in the genome but in the outer space. Consequently, the neuron looks unique in possessing a double memory - genetic and nervous. Equally interesting is the fact that, while DNA conserves the program of the species, the neuron accumulates engrams which have value for the individual. The engrams are realized in the compass of a specific phenotype but also can be indirectly involved in evolution as components of fitness. The genetic code is accomplished entirely at the chemical level, while the nervous code is constructed of physical and physico-chemical components. The nervous codification appears to begin and end with physical processes, while the chemical part has to do with the conservation of the engrams in a structure. To understand this arc, particularly the memory language, the XXIst Century and, likely, a large part of the Third Millennium will be needed.

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