Understanding the human brain: Need for a multidisciplinary approach

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Recent advances in diverse fields of science, from molecular to the behavioural aspects on one hand and mathematical modelling, artificial intelligence and computer science on the other, provide unparalleled opportunities to unravel the mysteries of the brain and may be the mind. This has been made possible due to developments in the techniques of molecular biology, genetics, tissue culture, neural transplantation, imaging coupled with advances in solid state electronics and computers. A brief account is provided of the current understanding of the biological basis of the functioning of the brain, outlining the need for a multidisciplinary approach to enhance this understanding.

NEUROSCIENCE research is a continuum of study from the molecular to the behavioural level. It encompasses the body of research directed towards understanding the molecular, cellular, intercellular processes – mediated through electrochemical signals, in the nervous system, integrated to subserve behaviour. As a matter of fact attempts are being made to bring within its scope illusive entities like consciousness and mind. Till recently, most neuroscientists, neuroanatomists, neurophysiologists, neurochemists, neuropathologists, worked in isolated discipline-bound compartments. It is now obvious that such an approach is no more conducive to unravelling the mysteries of the brain and mind. Rapid developments in diverse fields like molecular biology, recombinant DNA technology, genetics, and biotechnology supplemented by techniques like neuronal tracing, tissue culture, neural transplantation, different modes of spectroscopy, chromatography, radioimmunoassay, receptor assay, etc. now permit investigations right up to the molecular level. On the other hand, newer imaging techniques – positron emission tomography (PET), nuclear magnetic resonance imaging (MRI) and *in vivo* spectroscopy (MRS), single photon emission computerized tomography (SPECT), now permit physiological, biochemical and pharmacological processes to be studied in the brain of conscious, behaviourally active, human beings. Simultaneous advances in mathematical modelling, systems analysis, solid state electronics have attracted a host of scientists to try and create artificial intelligence. It is, therefore, not surprising that neuroscience has become one of the most attractive fields of research all over the world. It has been claimed that 95% of what we know today about the brain has been learnt in the last decade.

Recognizing the importance of this field, DST and DBT, Government of India, have identified Neuroscience as a thrust area. A number of major programmes have been initiated. However, we still lack a critical mass of scientists. Worse still, most investigators in the country, even today, work in isolation. The clinical neuroscientists have very little exposure to basic neurosciences. The basic neuroscientists work in discipline-bound compartments. There is hardly any dialogue between the neuroscientists and the molecular biologists, cell biologists and biotechnologists. The life scientists and the physical scientists – the mathematicians, the physicists, the chemists, the computer scientists are hardly able to understand each other's language. The two streams separate very early in our educational system. There is no forum or occasion for them to interact. The Programme Advisory Committee (PAC) on Neurobiology, therefore, decided to make a beginning by organizing this meeting. We have here with us some of the most distinguished scientists representing most of the disciplines mentioned above. We hope our interaction during these three days will pave the way for a better understanding of each other's expertise ultimately leading to creation of interdisciplinary groups willing to advance the frontiers of neuroscience research.

Here I provide a glimpse of the current state of our knowledge of neurobiology primarily from the perspectives of a clinician and a broad overview of the structure and function of human brain.

The basic unit of the nervous system is a neuron. It consists of a cell body (the soma) and processes (the dendrites, the axon) through which it gets its (sensory) inputs from other neurons and transmits its messages to the effector organs, muscles, glands or other neurons. It has been variously estimated that there are approximately 10^{11}–10^{12} neurons in the human brain. On an average each neuron is connected to about one thousand other neurons. The point of contact between the two neurons is called a synapse (Figures 1 and 2). Some neurons are reported to have as many as 200,000 synapses. A whole range of techniques are now available to study the morphological details of any

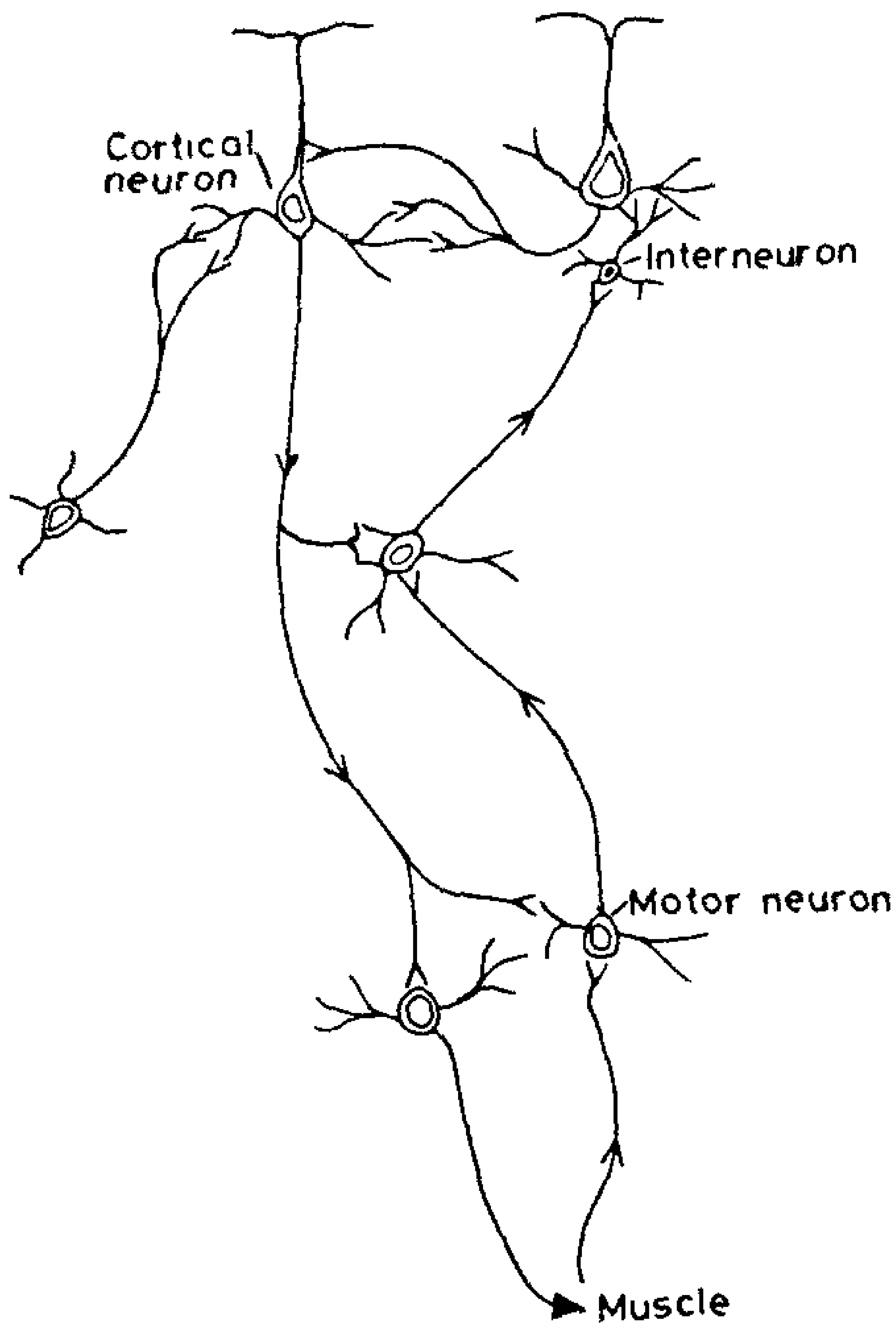

Figure 1. Sketch to illustrate a simplified neuronal network effecting muscular activity

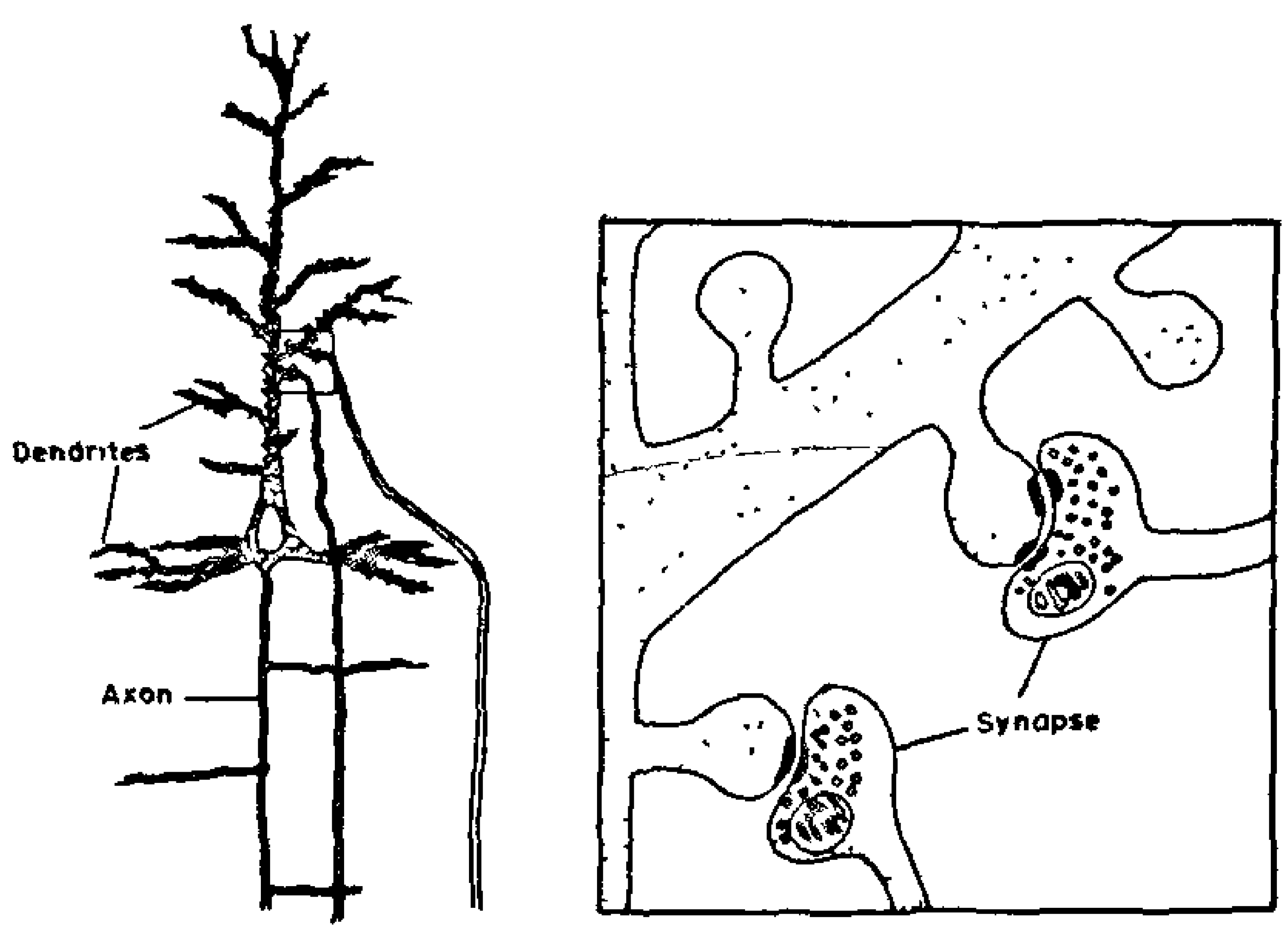

Figure 2. Diagram showing a full neuron with synaptic connections on the left and details of the synapses on the right (modified from *Sci Am*, September, 1992)

individual neuron or neuronal groups. While light and electron microscopy provide structural details at the level of subcellular organelles and synapses, immunohistochemistry identifies the specific neurotransmitters. Aesthetically elegant as these studies are, it is obvious that it may not be possible to analyse the more complex functions of the brain from the study of single neuron or even a group of neurons. The belief that the human behaviour or mental functions are nothing but a sum total of the neuronal activity of the brain has been already challenged by those who believe these to be the emergent property which is more than the aggregated activity of groups of neurons.

A variety of neuronal labelling techniques help trace the neuronal circuitry. These studies have provided valuable information on the structural basis of functional organization of different types and groups of neurons. Detailed maps are now available for some of the functional groups like those concerned with vision or motor control. There are several other systems, specially those concerned with cognitive functions, which are just beginning to be explored.

It is important to realize that much of neuronal circuitry which develops in an orderly, sequential and specific manner during foetal development is genetically determined. This may be compared to 'hard-wired' electronic circuits. However, a vast majority of neurons possess inherent plasticity which enables them to make (or break) new connections under the influence of environmental and behavioural inputs. It is this dynamic characteristic of the nervous system which is a nightmare for the electronics engineers who wish to model their computers and artificial intelligence on the pattern of the brain.

It is now well-established that the interneuronal communication is an electrochemical phenomenon. During the last decade and a half several dozen neurotransmitters and neuromodulators have been identified. The study of their synthesis, storage, release, degradation and recycling has provided a fascinating picture of the chemistry of the brain. At the molecular level, a number of receptors have been identified and some have even been cloned, sequenced and synthesized. Similarly a variety of ion-channels, which ultimately determine the generation and propagation of the electrical impulse have been identified and characterized. Information is now available on the physical, biochemical and functional features of some of these channels which ultimately determine the excitatory or inhibitory state of the neuronal membrane or even a part of it. It has even been possible to model these channels *in vitro*. These biochemical phenomena add to the ability of the neurons to vary their functional capabilities from moment to moment (Figure 3).

Electrophysiologically the neurons are as a rule supposed to behave on the principle of the 'all or none' phenomenon i.e. the electrical potential generated should reach a certain threshold before it develops into a discharge. The potential so generated is maximal and is capable of propagation. However, this basic characteristic can be influenced by a variety of phenomena like the state of resting potential, refractoriness, facilitation, recruitment, excitatory or inhibitory inputs from other neurons in the circuit. The earlier simplistic view of

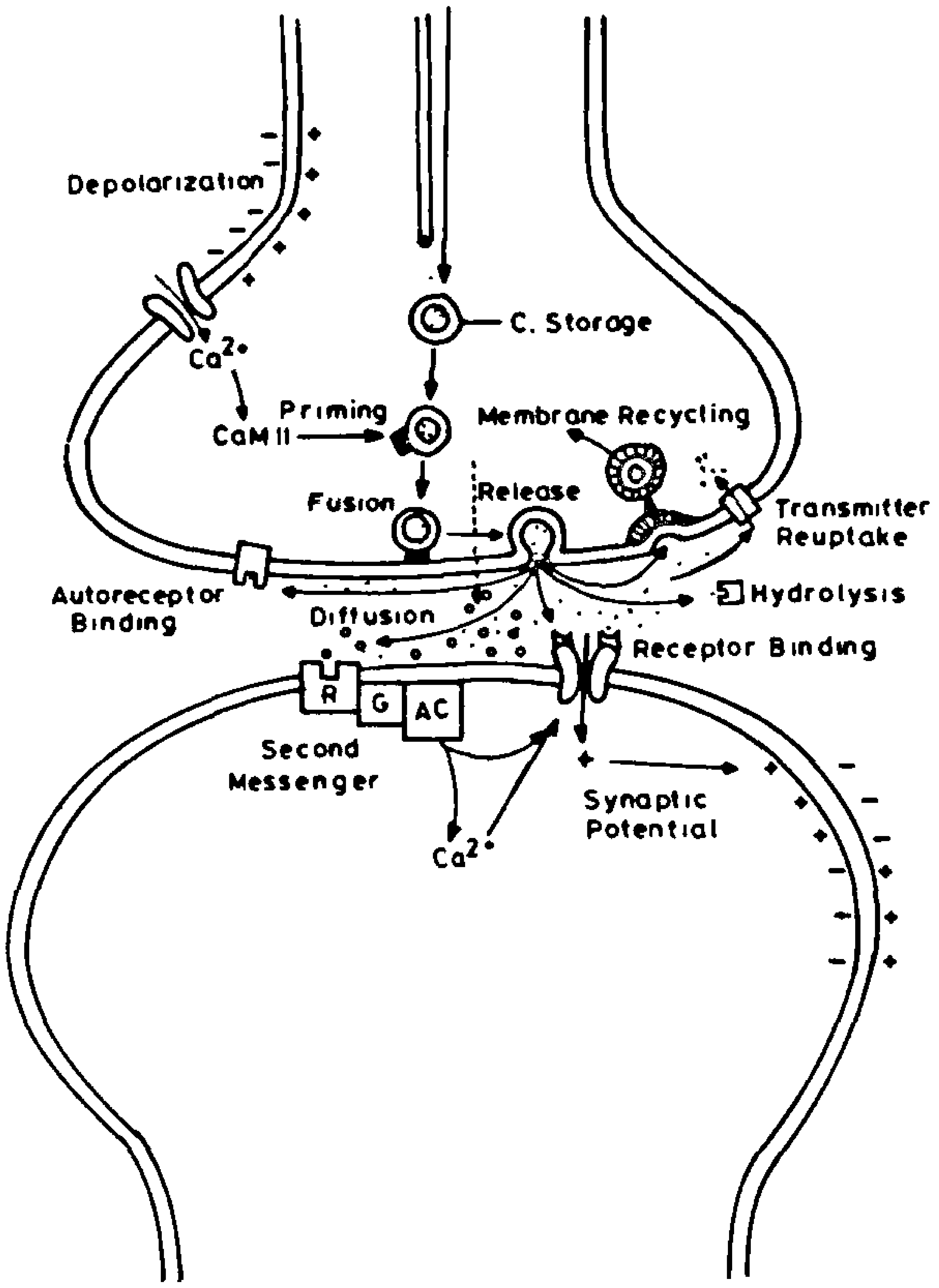

Figure 3. Diagram summarizing some of the biochemical mechanisms at a chemical synapse. AC, Adenylate cyclase, C, storage – Neurotransmitter storing vesicle; CAM II, calcium–calmodulin dependent protein kinase II; G, G protein, R, receptor. (Modified from *Neurobiology*, Gordon M Shepherd 1958)

neuron has already been replaced by a more complex reality. It can no more be viewed as a simple logic gate. It is analogous to a complete computer chip. It possesses a remarkable morphological and physiological flexibility. The diversity of neurotransmitters, neuromodulators, the ion channels, second messenger systems all constitute the individual player in an orchestra using the neuronal membrane as the stage. We know a lot about the individual player, we still do not know enough about how they combine to produce the symphony of purposeful neuronal functions. It has been estimated that during each moment of daily life neural signals may be transmitted across any of approximately 100 trillion synapses. The repertoire at the command of the nervous system to regulate its own function is rich, but how these neuroregulatory systems are organized still remains to be explored. Thus in actual functioning even the simplest neuronal circuit possesses a dynamic property not amenable to easy modelling. It may be mentioned that interneuronal communication is not just a matter of one-to-one direct contact between the two neurons (i.e. monosynaptic) but generally a complex networking with intervening multiple relay systems, in other words, a multisynaptic system. An impulse generated in one neuron, during its propagation to the target neuron/organ can thus be subject to modifications at several levels. At each of these levels there may be feedback loops to further modulate the propagated impulse. It is well-established that the electro-chemical properties of a neuronal circuit could be influenced by frequent use or training or repeated stimulation (kindling), so as to enhance the ease of communication, make the discharge repetitive or even self-perpetuating (long term potentiation). This has great relevance in respect to mechanisms for memory on one hand and epilepsy on the other.

Functional localization

Notwithstanding all the complexities mentioned above, the miracle is that such a complicated network of neurons is ultimately able to subserve precise functions, and respond to the changing environment and execute complex voluntary acts virtually instantaneously. The concept of functional localization in the brain began with Broca's identification of speech area in 1861. This was experimentally demonstrated in animals by Fritsch and Hitzig[1] for the somatic motor function. Penfield's studies of electrical stimulation of human cortex in conscious patients undergoing surgery for epilepsy under local analgesia elaborated this in great detail[2] (Figure 4).

Specific regions of the brain subserve various sensory–motor functions. There is somatotopic localization of these functions in distinct areas of the cortex; representing different parts of the body, e.g. face, fingers, thumb, arm, trunk, leg.

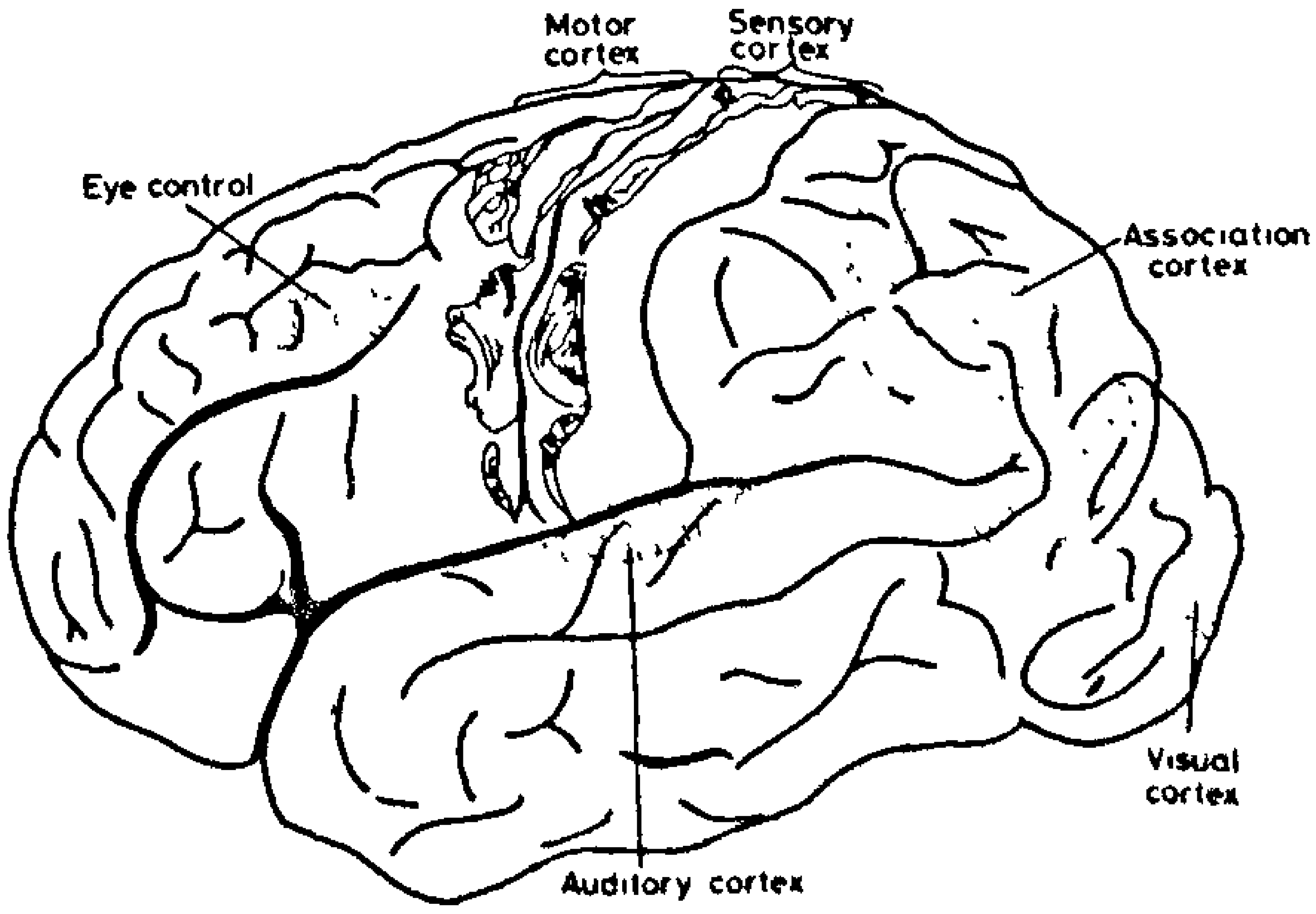

Figure 4. Functional areas of the cerebral cortex Body parts shown represent the areas of the cortex responsible for motor and sensory functions

The right half of the body is represented on the left side of the brain and vice versa. However, speech is generally localized in the left hemisphere in 98% of right-handed persons and approximately 60% of the left-handed persons. Largely because of the representation of speech in the left hemisphere it has come to be called the dominant hemisphere. However, it is now well established that the two hemispheres may be split into two largely independent cognitive systems, the left mainly subserving verbal and analytic processes and the right nonverbal, visuospatial, gestalt or holistic aspects. While we comprehend speech with the help of the left hemisphere, we appreciate music with the right. The visual, auditory and olfactory regions of the cortex are clearly defined. There are general indications of the parts of the brain involved in complex functions like sensory perception, information processing, memory, attention, learning, drive and emotion. The organization of these functional areas has been further elaborated to the level of individual columns of cells, and to individual cells within the column having a very specific repertoire of function, as has been demonstrated by Mountcastle[3] and Hubel and Wiesel[4]. Thus there are neurons in the cortex which are only activated when a particular profile, front or side, of a face is presented to the subject. It is no surprise then that it has been suggested that there may be 'grandmother' neurons, i.e. those neurons which respond only to the face of the grandmother! While the visual system has been the most intensely studied, information is gathering on the other systems as well.

There are large parts of cortex, like most of the frontal and temporal cortices, which do not appear to subserve any specific topographically organized function. It has been called the 'uncommitted cortex' or 'association area' by some, while Penfield[5] called parts of this as the 'interpretive cortex'. As a matter of fact the area of cortex in this category is much larger than that for which specific functions are known.

We seem to know more and more about smaller and smaller units of the nervous system, it is amazing that we are still a long way from understanding the integrated function of the human brain. We continue to look for the seat of consciousness, which even defies definition. Cobb[6] argued that 'It is the integration itself, the relationship of one functioning part with another, which is mind and which causes the phenomenon of consciousness'. How, where and by whom this integration is carried out is as little understood today as 40 years ago when this profound statement was made. Consciousness, no doubt, includes awareness, attention, cognition, discrimination, memory, responsiveness and volition, which can be quantified and measured. It also includes the inner-sensations, feelings, percepts, concepts, imagination, intuition, creativity which still defy objective study. Some of the most outstanding scientists of this century, like Sperry[7], Schrödinger[8], Wigner[9], Penfield[5], Popper[10], Wald[11], Penrose[12] and Elliott[13], found it impossible to explain consciousness or mental function on the basis of the existing knowledge. There are, nevertheless optimists like Crick and Koch[14] or Carla Shatz[15] who believe that all aspects of mind including its most puzzling attribute – consciousness or awareness – are likely to be explainable in a more materialistic way as the behaviour of large sets of interacting neurons. I have recently attempted to summarize some aspect of this vexed problem[16].

Notwithstanding the voluminous information already available in respect of the structure and function of the brain, the debate continues whether the different regions function as independent units like the units in a parallel processing computer or as a holistic system. It has been postulated that brain maps arise when computations are distributed across multiple processors of a parallel computer. However, to date there are no general guiding principles for relating the structure of a brain map to the properties of the associated computation[17]. Different regions or functional units of the brain utilize different computational strategies. Fundamental differences in the organization of digital computers and the brain make it difficult to translate ideas from parallel computing directly into a neural equivalent[18]. In any case one does not know the precise mechanisms involved in information processing, storage, retrieval, analysis and integration, ultimately leading to cognitive function or voluntary behaviour. A number of models have been proposed by neurobiologists, behavioural and cognitive scientists. Likewise mathematical modellars, computer scientists, systems analysts, neural network, and artificial intelligence experts are attempting to develop models to mimic the human brain.

Current approaches to study

Studying simple systems like *Caenorhabditis elegans* or *Drosophila* for understanding the principles of neurogenetics, or simple paradigms of behaviour like echolocation in bats, learning in bees or even simpler startle or righting response in still lower species in the hope of ultimately understanding the complex structure and function of the human brain, no doubt provides valuable data. Combining genetic approaches with single channel recording and techniques of molecular biology in *Drosophila* to understand organization of functions like smell or taste as is being carried out at Tata Institute of Fundamental Research, Bombay, are a good example of such studies. Others are attempting the study of cognitive functions in primates to elucidate some more complex functions like how primates perceive the world around them and store and later access information about it, how they plan and carry out actions upon the external environment, how they learn to modify behaviour in the light of past experience.

Answers to such questions cannot be found in the neurobiology of simple brains.

Methods for directly visualizing living processes in real time in experimental animals using video-enhanced microscopy and voltage sensitive dyes are being utilized to answer some of these questions. Phenomenal advances have already been made in imaging technologies which enable one to study higher mental functions in conscious, performing human beings utilizing PET or functional MRI scans. Areas of the brain participating in functions like reading simple alphabets or random words or sentences or nonsense script have been identified. Similarly, the region of the cortex involved in intention to move or actually voluntarily moving a part of the body are being delineated. Studies are underway on more complex intellectual functions. No doubt future technological advances would permit study of more complex behaviours. Optimists believe that the 20th century which has witnessed the unravelling of the atom and the gene may also see the mystery of mind resolved. Whether this dream is realized or not, it is true that the journey towards that end will be expedited by sharing of the expertise of diverse groups of scientists like those participating in this symposium.

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Neuromorphology

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Information is processed, focused and disseminated in the nervous system by neurons connected in serial and parallel pattern. These connections are either discrete or diffuse. Most of these neurons and their connections can be traced physically by various techniques using dyes, antibodies against neuronal chemicals radioisotopes and scanning. This has helped in reconstruction of the neural network and also to create computer programs of brain network for discrete functions and intelligence.

BRAIN is the most complex of all the organs. To comprehend how the brain controls thinking, feeling, learning, memory and other functions, one has to understand the anatomy of the brain, or more scientifically termed, the central nervous system.

Each function of the brain can be broken down into an enormous variety of activities. Each activity has different components and each component requires integration of a number of cells or neurons. This forms a unit or a module. Each module has a characteristic connection pattern consisting of the input, the output and the interconnecting neurons. Neuron forms the functional unit of the nervous system. It has a trophic centre, which is the cell body, with the nucleus and processes which extend short or long distances from the cell body. Processes make contact with other neurons or organs or tissues in the body for integrating and controlling functions.

According to Brodal[1] structural organization of the central nervous system exists in an orderly manner. Groups of neurons subserving a single function are organized at different hierarchical levels. Though each group subserves a special function in the broad sense, each neuron of the group has primarily a particular role. This is easily understood from the location in relation to other neurons in the same functional group and also in other related functional groups, connections and the chemicals synthesized for transmission of impulses.