INDIAN STATISTICAL INSTITUTE

TWENTYTHIRD CONVOCATION ADDRESS

Genes and Brain Circuits

by

Obaid Siddiqi, F.R.S.

Tata Institute of Fundamental Research, Bombay

24th January 1989

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Mr. President, Mr. Chairman, Professor Ghosh, graduating students, ladies and gentlemen

First of all, I would like to congratulate the graduating students on this very special day when they complete their education at the I.S.I and are ready to begin their professional lives. My young friends you are very fortunate because you go out into the world from an institution with the best of credentials. I wish you a fruitful and enjoyable life.

I feel very honoured that Professor Ghosh has chosen me to give the 23rd convocation address at the I.S.I. My own qualifications to address a gathering of accomplished statisticians, in the wake of a galaxy of distinguished predecessors in previous convocations, are minimal. I will therefore, seek your indulgence and begin with a personal reminiscence. Twentyeight years ago I was in the same situation as some of you might be today, looking for a job. Professor Mahalanobis gave me a pleasant surprise and offered me one. He called up the MRC Laboratory at Cambridge, where I then was, and left a message asking me to get in touch with him in London. My wife and I went to meet him in Hampstead where he was staying with a friend. We had a long conversation. It was not really a conversation but a monologue. Professor Mahalanobis talked to us about the nature of statistical science and his vision of the role of Indian Statistical Institute. Statistics as he put it, was not a mere mathematical theory. It was an experimental science akin to all experimental philosophies. It had the closest of connections with all experimental sciences and should best thrive in an environment where it rubbed shoulders with other sciences. That is why Professor Mahalanobis wanted, in the Indian Statistical Institute, a sample of every other science including molecular biology. Professor Mahalanobis dwelt at length, on the spirit of the Greeks that permeates Western science. He passionately felt the need to infuse Indian science, or for that matter, all Indian intellectual life, with something of the bold Ionian spirit of dispassionate enquiry. As you might imagine, my first and only meeting with Professor Mahalanobis has left a strong impression which I recall with warmth and admiration.

The research at I.S.I ranges broadly over statistics, mathematics, physics, earth sciences, biological sciences and social sciences. So it should not be out of place for me to make a few remarks about certain aspects of my own interest, in genetics and neurosciences. I will discuss the relationship of genes to brain. In recent years our knowledge of the vertebrate brain has improved vastly. So has our understanding of the gene. One can, therefore, talk about the age-old problem of nature and nurture in a more meaningful way than was possible hitherto. That is what I propose to do.

Any discussion of our own behaviour in relation to our genes can be easily bogged down in a medley of fears and prejudices. We must put these out of the way. Most progressive and egalitarain philosophers who believe that the human condition can be greatly improved, tend to think of the human brain as infinitely maleable and educable by nurture. By contrast, the defenders of the "status quo" are inclined to attribute all inequities to nature. These positions, at least in the minds of the lay public, have hardened to a point where a reasonable discourse is difficult. J.B.S. Haldane, a former member of this Institute once wrote an article entitled, "The Inequality of Man". Haldane argued that, as a geneticist, he knew that men were not born equal. The reason he was a socialist was that he wanted these inequalities to be mitigated. He was against capitalism because he did not like the clever-born to take undue advantage of their genes.

The issue I am going to bring up is not whether genes have anything to do with brain and behaviour and whether all humans are the same. The answers to these questions are already known. I wish to discuss a somewhat different and, in many ways, an unsettled problem. It is commonplace that vertebrate brain is very complex. Some feeling for this complexity can be gained by considering the number of neurons and their connections. Each one of us has more than ten billion neurons and somewhere between a ten trillion (10^{13}) and a thousand trillion (10^{15}) synapses. These are astronomical numbers. There is overwhelming evidence that the organization of the neurons and their mutual connections, the so called circuitry of the neurons, is very orderly. If it were not, our behaviour would not be so predictable. How is this intricate structure put together ? The brains of mice and men are pre-ordained to be similar in some respects and different in others so that their genes must provide the specificiations. But how do the genes manage to do this ? How indeed can they manage to put together this extraordinarily complex structure in all its functional glory. In the parlance of neurobiology, this problem is called the problem of neural specificity.

Our ideas about neural specificity have undergone radical changes in the last few decades and are still in a fluid state. The picture of a pre-ordained hard-wired brain was a natural outcome of the neuron theory of Ramon-e-Cajal, which took shape towards the end of the last century. Yet the dominant view of brain development, until the 1930's was quite different. It was believed that the brain of vertebrates is a coenocytic net in which every element is connected to every other element. Orderly structure in this formless "porridge" was believed to be impressed by function as a consequence of experiential inputs. This view of structure claimed to account for the adaptiveness of brain architectre and its remarkable ability to deal with the inputs from the external world.

The maleable "porridge" theory of the brain was demolished in the early forties by the monumental experiments of Roger Sperry on the formation of neural connections. For example, in a classical experiment with salamanders, when the developing eye was surgically rotated by 180^0, the growing optic fibres formed connections with their preordained targets, even though these connections were now maladaptive. Behavioural experiments showed that the salamander could not adjust to its upside-down world and its visual experience played no part in determining the orderliness of retinotectal projections. Sperry formulated the "chemoaffinity" theory of neural connections according to which each growing axon carried a chemical label which enabled it to recognise a specified target by a "lock and key" fit. The chemospecificity hypotheses has dominated our thinking about neural connections in the past fifty years. In addition to "address" and "name plate" molecules, other chemical guidance cues had to be postulated which enable the growing axons to grow in the right directions and to the right places, maintaining correct order. A major concern of contemporary molecular neurobiology is to identify and characterise these chemical cues.

Neural development, according to the views that prevailed in the fifties and sixties, was a fairly deterministic process, neurons and their connections being specified rather precisely and rigidly by genetic and molecular mechanisms independently of experiential inputs. This picture was reinforced by the remarkable anatomical and physiological experiments, pioneered by Mountcastle and Hubel and Wiesel, which revealed the intricate columnar orga-nization of the cortex and showed that the neural circuits required for perception of form were present in the brain at birth. All of this added up to the impression of a fairly rigidily designed hard-wired computer produced under strict genetic control.

In the last ten or fifteen years our views of brain circuits have begun to undergo a second revision. It now appears that the formation of neural connections in the brain of vertebrates is a dynamic process. It involves a close interaction of genetic and epigenetic factors and not simply a wiring of rigidly identified elements. It is now known that, during development, many more axons project to target neurons than are finally found in the adult brain. The excess of neurons and synapses is finally eliminated. The elimination of supernumery axons and synapses involves a competition between contending neurons. The outcome of this competition is profoundly influenced by external input. Consider the optic fibers projecting from the two eyes. The input from either one influences the size and pattern of projections from the other. The pattern of connection is substantially altered, if during a critical period of development, visual input from one of the eyes is blocked. It is this intimate interaction between genetic endowment and plasticity that underlies the adaptation and fine tuning of neural circuits to the complexities of the external world. Gerald Edelman has called this process neural Darwinism.

It would seem that the strictly defined target recognition mechanisms visualised by the early versions of the "chemoaffinity" hypothesis, have to be replaced by a more dynamic, interactive process. There is growing evidence that the rearrangement of neural connections is modulated by trophic influences exerted by the target neurons. The role of these target-derived synaptogenic factors came to light through the discovery of the Nerve Growth Factor (NGF) by Rita Levi Montalcini and Victor Hamburger. NGF is produced by target cells. The axons terminating on these, develop NGF receptors and take up these molecules to transport them to the cell bodies. It has been found that NGF also modulates the branching of the axon terminals and the formation and maintenance of the synapses. One is thus, dealing with a feed-back regulated dynamic interaction and not merely the recognition of a narrowly specified molecular "name plate".

The elucidation of the fundamental molecular mechanisms for modulating neural connections is a major challenge before molecular biologists and neurobiologists. In particular this issue is the *raison d' être* of my own field, neurogenetics. Much of neurogenetic research is, at present, done with lower organisms such as fruitflies and worms. In lower organisms, neural development is pre-ordained to a greater degree than in mammals and birds. In these animals, the formation of specific connections is often predictable at the level of single neurons. The question arises, are the fundamental mechanisms for modulating neural connections, the same in higher and lower animals. My own inclination is to answer this question in the affirmative. But I do not know. Only time and further research can provide the answer.

The issue which I have raised has many practical implications. In particular it directly affects approaches to neurosurgery and treatment of congenital neural disorders. It must also influence our approach to psychiatric illness. On a purely scientific plane a correct understanding of the formation of nerve connections is essential for a deeper understanding of perception and cognition and in general, of all other things that our brain does.

I hope I have not taken too long, and have not taken you too far from the more pressing concerns of our lives. It is common these days, to berate the scientists for applying themselves to abstruse pursuits and for living in "ivory towers". In this respect, as statisticians, you are more fortunate than the rest of us. The very nature of your science will keep you close to everyday life in our country, people, politics, economics and the environment. But the science of statistics has a deeper connection with the world through its concern with the notions of probability, uncertaintly, order and information. The very same concepts connect your science to artificial intelligence, and to brain and its function, perception and cognition. I therefore wish and hope that some of you will develop an interest in the subject to which I have drawn your attention but at any rate many of you will devote your energies and talents to continue the pursuit of knowledge for which your excellent training at the I.S.I has prepared you.

I congratualate you again and wish you a full and satisfying life.