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Epigenetics, Biotechnology, and Other Scientific Advances: The Role of Iraqi Researchers

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Abstract: The past two decades has witnessed an amazing outburst of scientific developments and discoveries accompanying the so-called Genetic Revolution. The advances that followed the deciphering of the Human Genome in 2003 particularly in the molecular biology and genetics were not possible without parallel developments in the biotechnologies and the bio-informatics. The new science of Epigenetics was developed in the aftermath with surprising revelations. In this article we will be examining the relevance of these developments to the Iraqi research and the problems of environmental pollution 1991-2004 with the consequent rises in cancer and birth defects. We submit a new theory that birth defects in Iraq are more likely to be caused by Epigenetic factors than carcinogenetic factor and we call for a well oriented and problem targeted planning in scientific research in Iraq. The successful themes in the scientific research of the 21st century are the culture of team work and co-operation and the integration of expertise among specialists. The American example of a highly successful, well planned and problem oriented team research work that lead to deciphering the human genome and the development of the science of epigenetics is discussed. The role of governmental support is illustrated. Recommendations and suggestions are made in the coarse of developing a problem oriented scientific research in Iraq such as to allow the Iraqi scientists to be ahead of other scientists in solving the Iraqi problems.

Key words: Epigenetics . Iraq. Malformations. Cancer. Biotechnology .

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Introduction

Some people think that it is not always good to be ahead of time, John-Baptist Lamark knew all about it. During the eighteenth century Lamark suggested that the long neck of the Giraffe was acquired because of generations of stretching up by its ancestors in order to reach the best nutritious leaves on tree tops. Those remarks were sufficient to ridicule the man for the rest of his life. Charles Darwin's theory of Evolution was much preferred, applying this, the Giraffe's neck was elongated in a slow evolutionary process successively selecting the better genes: those of a longer neck. Gregor Mendel who died in 1884 worked his experiments in genetics in line with Darwin's theory and so we learned at schools and universities that we inherited a (*genotype*) from our parents which is dictated and controlled by (genes) in a fixed and unchangeable manner (nature), and that we acquired a (*phenotype*) after birth from the environment e.g. habits, lifestyle, social interactions and education that expires with death (nurture).

The American biologist Barbara McClintock was much closer to the

concrete facts. In the fifties of the 20th century, she described the theory of (jumping genes) to explain the color varieties of corn seeds on one single head of an American corn (the wild species of the common yellow corn). She suggested that genes may change their position (transpose) during mitosis and called those genes (transposons). Much as she was right she was treated like Lamark until her work was finally recognized such as to win her the Nobel prize in 1983. Other scientists (rediscovered) the (transposons) later as (transposable elements) and (metastable alleles) (6,12).

In fact Lamark and Darwin were both right as the most recent research findings in the molecular biology, and genetics shows except that no one knew about the presence of a direct link between the genotype and the phenotype in their days.In fact the real domain of the ongoing process of evolution appears now to be this link (and not the genes), the so- called *Epigenetic reactions.*

What Is Epigenetics?

Epigenetics is studying the link between the genes inside the nucleus and the environment outside it whether it is within the body or externally. It developed fast in the years 2000 when the biotechnological techniques became sufficiently advanced such as to enable scientists to study the Histone protein (tight package) membrane around and within the DNA helix in the chromatid and its reactions with external modifying factors nowadays called the *(Epigenes)*. This wrap is regularly interrupted along side the DNA strand dividing it into units: (the *nucleosomes*) and leaving areas of exposed (link-DNA) in between. The *Epigenome* is the combination of all genomic wide chromatin modifications in any given cell type that directs its unique gene expression pattern (4).

Internal body changes (such as a toxic elements in the blood circulation, disease, or trauma) (4,5) or external distinct environmental factors e.g. famine, or exposure to a toxic or carcinogenic substance) (10,13) may cause an (epigenetic reaction) anywhere along the nucleosome. At least three types of epigenetic reactions are described to date :(Histone modification) by adding a chemical group e.g. methylation, acetylation, phosphorylation and other reactions, covalent methylation bond within the DNA helix usually at a Cytosine – Guanine link, or the modification of RNA species which plays an important rile in the transcription of gene expression. These reactions affect the directly adjacent genes either by silencing or by enhancing their expression, and by doing so changing the total gene expression product inside the cell (e.g. the types of protein building amino acid units) which will manifest in changes in cell growth and differentiation directly attributing to the (phenotypic) variability between individuals and to their disease susceptibility (Figure-1).

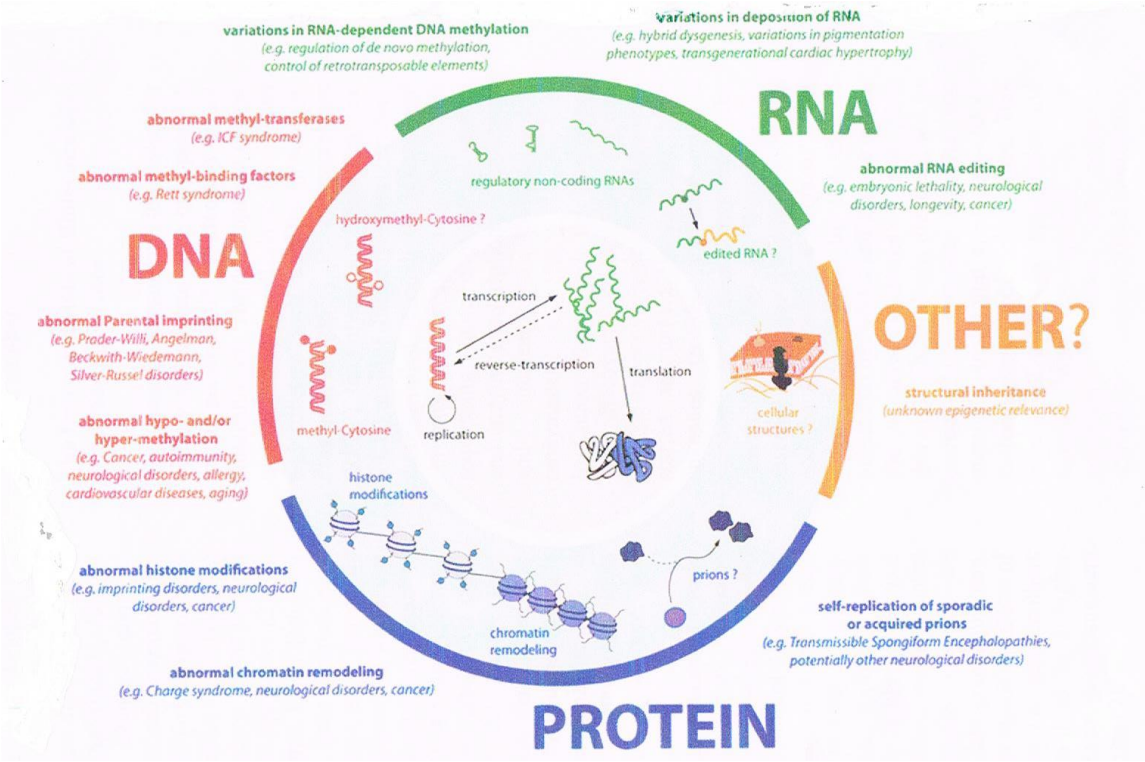

Figure1:The Duality of Biological Information:Genetic and Epigenetic **http://www.discoverymedicine.com/Richard-Chahwan/2011/03/17/the-multidimensional-nature-of-epigenetic-information-and-its-role-in-disease/**

An epigenetic reaction may take place in each individual cell separately (6) (think of McClintock's colorful seeds on a single head of American corn), or in a specific group of cells as a matter of functional adaptation (11) (which may explain the anatomical and physiological differences between body organs which carry the exact genome).

This way, genetic expression and its cellular products will be changed by (controlling) gene activity without changing the gene sequences. One may compare the genome to a piano key board with a fixed set of keys producing different tunes when playing different keys. The player is the epigenetic reaction. The genome is in fact fully controlled and directed by the epigenome. In functional terms while the genome plays a role during cell reproduction (mitosis and meiosis) the role of the epigenome starts thereafter during cell growth and differentiation.

The most interesting finding is that some epigenetic changes can be mitotically and meiotically heritable (8). An *(Epigenetic trait*) is defined as *a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence* (2).

A mother's exposure to an (epigene) such as hunger or a toxic chemical even prior to pregnancy may leave its (imprints) on her epigenome which can be transmitted later after pregnancy to the zygote and maintained as a (parental

imprint) in the foetal primordial cells, the precursors of the fetus's own gametes. This means that the adverse effects of a one- time exposure to a toxic or carcinogenic epigene may be inherited for at least three generations after exposure (mother, children, and grandchildren).

Sex-specific transgenerational epigenic effects are also possible in the male–line. One study shows that fathers who start early smoking (before 11 years of age) seem to produce sons with a high Body Mass Index at their 9^{th} birthday but this does not apply to their daughters. Similarly, a history of poor nutrition in a grandfather was associated with a high mortality rate in his grandsons but not his granddaughters. The study found the opposite effects of nutrition in females i.e. grandmothers with poor nutrition lead to a higher mortality rate in their granddaughters but not their grandsons (7).

Therefore Epigenetic changes can be:

- Influenced by environmental factors
- Heterogynous in cells
- Different between health and disease state in an individual
- Different from one generation to another

The Important Role of Biotechnology in Advancing Science

The scientific advances in the molecular biology and genetic were only possible in the presence of advances in the biotechnology. The development of new biotechnological methods in the eighties and nineties such as The Restrictive Fragment-Length Polymorphism (RFLP), the Polymerase Chain Reaction (PCR) and the Electrophoresis, enabled more detailed research on cellular and chromosomal levels such as DNA sequencing, gene expression, protein and enzyme transcriptions, intracellular and nuclear metabolism and biosynthesis.

In Cancer Research , the *Oncogenes* were discovered in the early eighties and the molecular basis of malignancies started to unfold leading to huge advances in the biopharmaceutical sciences and drug research. The research expanded to include other diseases of genetic and immune origins and the synthesis of a range of novel drugs that answers to the disease process on molecular and genetic levels, the so-called (immune – and gene therapy). These drugs are designed to correct the enzymatic, immune and metabolic errors that are the results of faulty expression of defect genes. This cascade of events in the eighties and nineties was accompanied by the necessary advances in computer science, bioinformatics and biostatistics. We stood at the verge of the Genetic Revolution.

As research in the genetics advanced after 2003 so did the development of innovative methods capable of analyzing the finest micromolecular structures. Methods like microdissection of biological samples, bisulphide treatment of DNA , gene specific bisulphide PCR, and Large scale sequential PCR amplicons were developed. Analysis was carried out by Mass Spectrometric micro array assay and even nanotechnology was used. New computerized biotechnologies were established and new statistical methods were developed resulting in huge advances in the bio informatics.

The Relevance to Research in Iraq

There is no doubt that molecular biology, genetics and particularly

epigenetic research should be of particular importance for Iraqi scientists. In the past 27 years an unprecedented amounts of radioactive and toxic *gene damaging* chemicals were deposited in international conflicts on and around inhabited areas causing important environmental and ecological pollution. In addition to the human disasters that unfolded the consequences of such pollution were manifested in unprecedented numbers of malignant diseases and congenital malformations as well as many other pathological phenomena and disease states which can be all related to genetic damage and/or environmental pollution. Most of these disease processes remains unstudied or methodically described due to the lack of attention, interest, and an organized and well directed research resources.

The effect of nutrition on the phenotype has been first reported in mice in 1978 (13). Researchers found that these effects could be corrected in successive generations with the proper dietary supplements (14). Following the scientific developments that lead to the discovery of the epigenic reactions it is now thought that some hereditary birth defects such as s*pina bifida* may well be due to environmental factors causing epigenic DNA methylation. This is supported by the fact that treatment of pregnant mothers with Folic acid (a demethylator) shortly before or during the first trimester of pregnancy help preventing this condition in the fetus possibly by removing the epigenic marker of DNA methylation.

The environmental pollution in Iraq has been found to include a number of chemical factors which could be traced back in the biological samples of parents with children with birth defects in the cities of Basrah and Falluja. These included known poisonous metals such as lead, arsenic, aluminium, copper, iron, cadmium, nickel, thalium and others. Researchers noticed that those malformations were of the folate dependent types (1).

Considering the epigenetic research findings above and the results of the research on birth defects in Iraq one may be able to conclude that the genetic birth defects in Iraq are likely to be caused by an epigenetic reaction to environmental pollution. This theory need to be explored further. The obvious possibilities of offering treatment and planning preventive measures are also to be explored.

In addition, the fact that epigenetic reactions were found to be able to silence or enhance gene expression changing cell differentiation points to their importance in cancer research. Normal cells acquire malignant characteristics largely as a result of the enhanced expression of an (Oncogene) and the silencing of a tumor growth suppressor gene resulting in poorly differentiated malignant cells (3).

Iraqi scientists are sitting on a wealth of scientific material waiting to be explored. They should be in the lead of other scientists in reporting, registering and documenting new and rare disease processes as well as conducting research which help providing answers and finding solutions to the enormous problems the country is burdened with rather than following a traditional line of research activities.

A Succesful Model of Research Planning

In 1990 The Human Genome Project was launched in the United States and several other countries simultaneously. The aim was to decode the human

genome in full. The first human chromosome to be completely decoded was no. 22. In 2003 the full *Homo sapiens* genome was decoded all complete with its 3 billion base pairs. From that point on the *Genetic Revolution* started and researchers continued to study the functions and behavior of genes in sickness and in health, the science of *(Genomics)* was born.

Between 1999-2006 the Human Epigenome Project (HEP) conducted its first studies to gain insight into the complex relationships between the genetics and the epigenetics that underlies both normal and disease state cellular homeostasis in particular auto-immune diseases. In addition to the USA countries like the UK, France, Germany, China, and Japan were also participants (Figure -2).

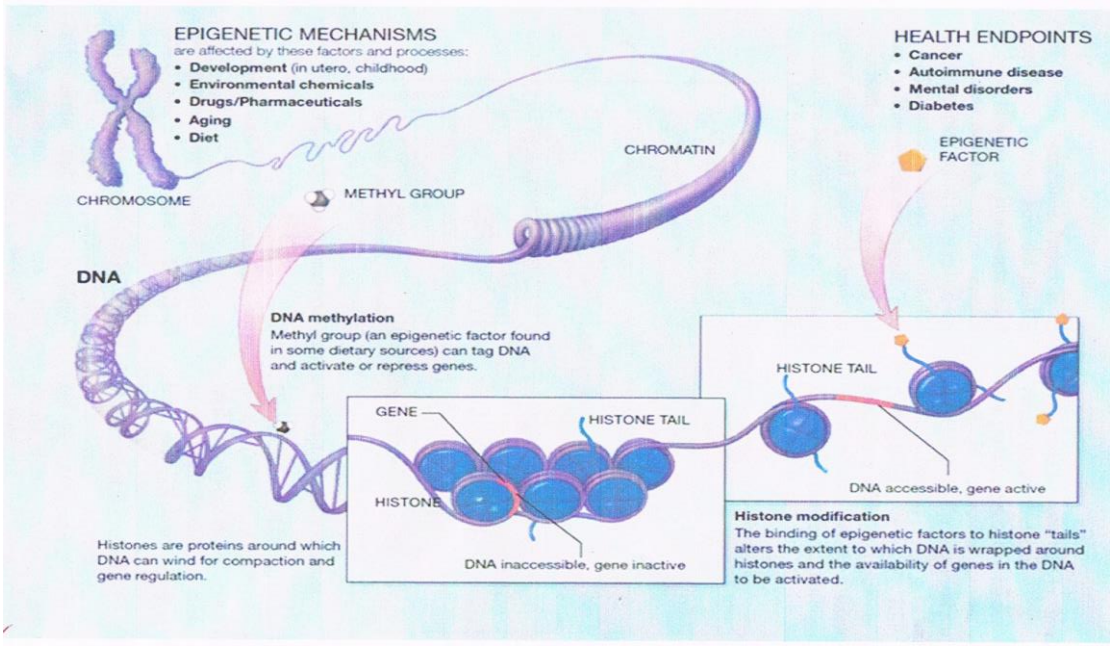

Figure (2) Epigenetic Mechanisms "by National Institutes of Health" http://commonfund.nih.gov/epigenomics/figure.aspx.

The US national institute of health (part of the federal department of Health) stated three targets: To develop new epigenetic assays, to generate reference epigenetic maps, and to describe disease specific epigenetic changes by then expanded to involve not only auto-immune diseases but also cancer, diabetes, and mental disorders based on the initial research results and supplying more funds towards the new targets.

The Human Epigenome Project is an example to illustrate how did the US National Institute of Health responded to the new needs to advance research and investigate initial facts based on primary research findings that resulted from the Human Genome Project. They announced a new project, stated its targets clearly and supplied funds to develop new biotechnologies in order to enable the further necessary research in that respect such as to investigate certain disease problems.

The participation of several countries in such an enormous project is an

illustration of the importance of team work. Despite this international participation in the HEP, our researchers seems to be absent despite the importance and direct relevance of this research to the country

Discussion and Recommendations

The unusual environmental pollution with toxic and gene damaging chemicals in Iraq that took place particularly between1991-2004 was manifested with unprecedented environmental and health problems raising questions that are still unanswered. There is a wealth of scientific and medical information to be studied , constituting new scientific evidence and advances related to the reaction of genetic and epigenetic systems to the damage caused by environmental factors.

Given the multiplicity of these factors and the likelihood of inheritance of their toxic effects such studies may constitute an important researching material for long years to come. For example, studying the uncommon disease phenomena and exploring the effect of environmental pollution on the genes and epigenes is not a once off study but should be followed-up for generations in order for the whole picture to be complete. Iraqi scientists have the opportunity to be in the lead in exploring what has happened and is still ongoing in Iraq in the light of the enormous scientific advances achieved in other countries of the world.

Meanwhile, the current environmental pollution in Iraq and the unprecedented health and other problems it caused are deteriorating while a significant amount of the pollutants and exposure to pollution remains on the ground and while no treatment or prevention plans are in sight.

These circumstances in Iraq calls for a common general research plan oriented to the national problems and targeted to provide explanations and solutions to them.

In other countries of the world such a common national policy plans are decided by the scientific departments of the governmental institutions in accordance with the governmental policies and budgets. They usually include a number of set up national and sometimes international targets. The universities in turn set up independently their research projects in line with these national plans involving their own variable scientific interests. Approving a research concept by a university department requires it to recognize the targets set up by the university which is usually reviewed annually.

In Iraq, leaving the governmental role aside, to reach directly to the universities and their faculties there is at the moment no perception of targeted research or a common plan which is oriented to the important national problems in existence. In addition scientific research in Iraq remain individual, erratic and largely personal. Scientific team work and collaboration are not obvious among Iraqi researchers. The 21st current concept of team work and integrated specialist expertise is largely unknown yet. This culture will have to change.

The priorities of importance in research has shifted currently towards the basic sciences such as the molecular biology and genetics and biopharmaceutical sciences as well as biotechnology and bioinformatica. These are hugely funded by governments and private companies.

Given the political uncertainties scientists in Iraq the need for national planning can be substituted for the time being with a common target plans directly at the level of universities and scientific departments. There may be a need of an Iraqi Universities Scientific League or a similar institution for the purpose of deciding and approving a common nationally oriented research and study targets. The universities would set up their own research projects in line with these targets each with the availability of their own experts. The faculties approve research concepts from their expertise also accordingly.

In addition, establishing a (biological bank) may be a temporary solution in order to keep abnormal and diseased biological samples of human, animal, plant and other origins in a properly preserved classified and labeled manner such as to be preserved for as many years as it may be necessary until the time comes when researching them will be possible.

Benefiting from the advise and expertise of thousands of Iraqi specialists residing outside the country should not pose a great challenge in the presence of communication technologies. Medical, Biological and Biotechnological research is a national wealth too.

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