EDITORIAL

MAKE SPACE FOR EPIGENETICS

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Psychiatrists are attracted to their field because they are interested in the way people feel, think and behave. We spend years leaning how to read the signs and symptoms of our patients - as haematologists do the cells they see in their microscopes. And, we learn how to use our own appearance and behaviour as therapeutic agents - how to calm the psychotic individual and encourage the psychotherapy patient.

But most of us still have the desire to be like most other types of doctors - to know what is going on at the molecular level. For us, progress at the molecular level has been slow. Our most potent intervention, electroconvulsive therapy, was first used in 1938. There has been progress in reducing side-effects, but after more than seven decades of continuous use, when the young anaesthetist (who knows exactly how his/her atropine works) asks, "How does ECT actually work?" – we shuffle with embarrassment and reply, "We only know it works".

There have been advances which have promised molecular revelations - when the human genome was deciphered our hearts jumped, but some years down the track we are only a little better informed, and more than a little disappointed.

Epigenetics will provide more. It promises to explain how, 1) the cells of different organs (liver vs lung) are structurally and functionally different yet possess the same DNA, 2) one X chromosome in every mammalian female is completely inactivated throughout life, 3) mothering behaviour in rodents is transmitted from one generation to the next, 4) the pups of good compared to poor rodent mothers have attenuated responses to stress, 5) early life stress predisposes humans to mental disorders, 6) traumatic life events trigger stress disorders, 7) different ethnic groups have different risk of PTSD, 8) 50% of monozygotic twins are discordant for schizophrenia, and 9) major depressive disorder becomes autonomous and the triggers of later episodes become less clear. It even suggests a new revolution in molecular treatment of mental disorders.

Epigenetics, like inflammation, is a rapidly developing, highly specialized field, and psychiatrists will have to make efforts to get in touch with advances. Perhaps annual conferences should include workshops where those of us who graduated years ago can learn new basics, in non-embarrassing settings.

Epigenetics refers to modifications of genetic material which cause increases or decreases in the expression of genes, in the absence of changes to in the DNA code. Such modifications may be transmitted across cell division and even generations. We are all aware of the basic structure of DNA, and that it is tightly packed to fit into the cell nucleus. What some of us have forgotten, or have never known, is that most DNA is wrapped around tiny clumps of protein (histones) which have short amino acid 'tails'. The combination of DNA and histone cores is called chromatin. The basic unit of chromatin is the nucleosome, which is composed of the histone core and 1.65 turns of DNA. When chromatin is tightly packed genes cannot be expressed, they are 'silent', but when chromatin is relaxed, transcription is possible and the genes are 'active'. A central feature of epigenetics involves the packing and unpacking of genes - allowing them to be switched from silent to active and back again.

At the moment we know of two main methods of changing the tightness of DNA packing.

Both involve the attachment of a biochemical molecule (called epigenetic marks) to chromatin. The main difference is site to which these epigenetic marks are attached. One is DNA. Usually, a methyl group is attached to a cytosine nucleobase at the C5 position, forming 5-methylcytosine. This usually takes place at a CpG site (where a cytosine is next to a guanine, separated by a phosphate). The process is catalysed by DNA methlytransferase (DNMT). The second site to which an epigenetic mark can be attached (often an acetyl group, but can also be a methyl group, ubiquitin or a SUMO protein) is a histone tail. This is often to serine or lysine components. This is catalysed by histone acetyltransferases (HATs) and reversed by histone deacetylases (HDACs). Whether an epigenetic mark will cause tightening or relaxation of chromatin depends on a range of factors including the state of the chromatin and the region (promoter, repressor, etc) of the attachment. Non-coding RNA also plays a role in epigenetics but will not be discussed here.

The nature of any epigenetic changes depend not only on the type of environmental experience but also the age (developmental stage) of the organism, and the region of the brain being examined. Changes in gene expression affect all parts of the organism but important to psychiatry are those which impact on the HPA-axis and neural plasticity genes, such as brain-derived neurotropic factor.

In classic studies Weaver et al [1] demonstrated that the pups of rat mothers who demonstrated high levels of licking and grooming (LG) and arched-back nursing (ABN), compared to those of low-LG-ABN mothers demonstrated different DNA methylation of the promoter of the glucocorticoid receptor (GR) gene, in the hippocampus. These offspring, as mothers, performed high-LG-ABN, and more modest HPA responses to stress. These authors then demonstrated [2] in the adult, by the infusion of L-methionine, that these epigenetic marks and associated behaviour, could be pharmacologically reversed.

Stressed rodents demonstrate hippocampal modifications – Histone 3 is phosphorylated at Serine 10 and acetylated at Lysine 14 (H3S10pK14ac) [3]. In humans, both childhood adversity and suicide have been associated with altered DNA methylation near several key response genes in the hippocampus [4]. The scene is set for a molecular understanding of PTSD [3].

Half the vulnerability to addiction is due to psychosocial stressors, of which the most important is exposure to the drug. Of prime interest is the mesolimbic system - the ventral tegmental area (of the brain stem) communicates with the nucleus accumbens (both of which are reward centres), hippocampus, amygdala and prefrontal cortex (all of which are involved in memory). Repeated morphine or cocaine administration produces long-term histone methylation in the nucleus accumbens [5], suggesting a mechanism for addictive behaviours.

As with addiction, a large proportion of psychotic disorders remains unexplained by genetic effects, and gene-environment interactions are being examined. Studies have not yet directly connected environmental experience, epigenetic marks and psychosis, but breakthroughs are anticipated. In an exciting recent study, Wocker et al, [6] performed a genome wide DNA analysis on post-mortem brain tissue from people who had suffered schizophrenia. They found almost 3000 differentially methylated genes. They also found two clusters, the first composed of 88% of patients and 12% controls, and the second composed of 27% of patients and 73% controls. This suggests epigenetics may offer diagnostic biomarkers of schizophrenia.

Therapeutic opportunities spring to mind, and some psychiatric medications have been shown to have epigenetic effects. Of enormous interest is the work of Perroud et al, [7], which has suggested the possibility of epigenetic marks being changed by psychotherapy.

The message of this Editorial is that epigenetics will be of profound importance in psychiatry, and it is time to start wrestling with the basics.

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