FOCUS: NEUROSCIENCE

Introduction

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Issue Editor, Yale Journal of Biology and Medicine, New Haven, Connecticut

Ever since Santiago Ramon y Cajal produced the first images of the neuron with its incredible complexity and diversity, the field of neuroscience has grown increasingly intricate and branched into hundreds of areas of study. Uncountable advances over the past half-century have given rise to an ever-deepening understanding of brain function and dysfunction, but have also revealed the many unknowns that remain. Perhaps the most pressing questions address what happens when brain function goes wrong and how this can be avoided or repaired. Our contributors for the YJBM Neuroscience Issue have approached this question in various ways, elucidating the contribution of synaptic changes, molecular mediators, and environmental factors to an assortment of neurodegenerative diseases. They propose diverse new avenues of research, both theoretical and methodological, to further the study of brain dysfunction.

The nervous system, with its enormous cellular diversity and functional sophistication, is particularly vulnerable to gene and protein disregulation. In many neurological diseases, proteins that perform important functions under normal conditions become destructive. In their review, McCarthy and Bhide describe how brain-derived growth factor (BDNF) function, normally crucial for learning and memory, can mediate addiction to drugs like cocaine. These drugs exert epigenetic effects on BDNF promoter activity, leading to overproduction of the protein and a variety of synaptic changes that contribute to addiction. Thus, researchers are becoming increasingly aware of the dual functions of individual proteins. One particularly striking example of this problem is examined by Rodgers and Miller in their review of multiple sclerosis. They describe the complex role of cytokines, molecules that mediate immune cell activation and infiltration into the CNS but also have a surprisingly protective role when expressed by neurons and glia themselves. Such dual function of many proteins in the heterogeneous brain environment makes treatment of brain disorders especially difficult.

One of the major challenges in understanding neural diseases stems from the fact that brain function arises from the numerous and complex interactions between many neural cells. Thus, any number of emergent causes may disrupt function, and these disruptions may be extremely difficult to detect. One example of a more straightforward brain disorder is described by Marinoglou in her examination of ataxia telangiectasia (AT). In this disease, mutations affecting a DNA damage repair protein causes neuronal death in the

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cerebellum and results in paralysis of the patient. However, in many other diseases like Alzheimer’s, neuron dysfunction, rather than death, mediates the pathology. Johnson and Lombroso describe a process of synaptic dismantling mediated by Striatal-Enriched protein tyrosine Phosphatase that is a hallmark of several brain disorders including Alzheimer’s, schizophrenia, and Fragile X Syndrome. This raises the possibility that these diverse diseases may be related by common molecular and functional pathways. The shared link between different neurodegenerative disorders is further explored by Patel, who associates impaired histone acetylation and synapse weakening to memory decline during aging, Huntington’s disease, and Alzheimer’s and points to a role for environmental enrichment in treating these disorders.

Our understanding of neural disease improves along with our methods for studying them. Millet and Gillette describe our progress from culturing neurons on a hanging drop to the use of complicated co-cultures and microfluidic devices that are allowing us to better mimic the neural environment in the culture dish and test drugs more effectively. Similarly, animal models for brain diseases are dramatically improving. Lucke-Wold and Huber describe how ischemic stroke models can be made more relevant to human patients. They propose models that combine high fat diets with knockout mice predisposed to hypertension, obesity, or diabetes. While cell culture and animal models are crucial for the advancement of neuroscience, the unique nature of the human brain requires equivalent advances in human research methodology. On this front, neuroimaging using PET and FMRI are at the fore. In their article, Kerr and Lau identify a novel signal-to-noise problem in measuring hypometabolic tissue using PET. Their study reveals that diseased brains may require specialized imaging and quantification techniques.

In a world with an aging population and improved health care standards, the quest for a better understanding of brain diseases is likely to continue to be the most important pursuit of the neurosciences. The vast diversity of approaches reflects the complexity of both the brain and the diseases that plague it. A glimpse of this variety can be found within the pages of this issue. Initially, this diversity within neuroscience presents considerable challenges; however, the wide range of knowledge required to tackle neurological diseases is necessarily multidisciplinary. This produces opportunities for unique partnerships across different fields and extraordinary innovations that are likely to continue for years to come.