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The WPA Section on Immunology and Psychiatry was created about two decades ago. That action was in recognition of mounting scientific evidence that the immune system plays a major role in the etiopathology of psychiatric disorders including aspects of the mode of action of psychoactive medications. The term Neuropsychiatry (NP) was introduced and used over at least the last 30 years; it was later expanded to include selected disorders including headache, neuropsychiatric lupus, schizophrenia, bipolar disorder, and even single substances, such as cannabinoids. Basic themes, such as neuroplasticity, neuroprogression and oxidative stress were later included in conjunction with neuroimaging, neurogenetics, neuroimmunology. The term Psychoneuroimmunology was coined to connote the area of research dedicated to understanding the fundamental interactions between the immune and nervous systems and ultimately gave rise to the introduction of the term "Immunopsychiatry". This is now recognized as a new discipline which conveys more succinctly how these two systems, along with others, such as the endocrine system, are intricately intertwined. The term Immunopsychiatry provides new insights into disease pathogenesis and opens up new avenues to pursue for the development of immunotherapies for major psychiatric disorders. Increasingly the term Immunopsychiatry is gaining wide acceptance, and, in this context, Section members discussed the adoption of this term to rename the Section. This decision was made at the WCP held in Vienna in 2023, and was subsequently approved by the members following careful consideration of alternative name options. Formal approval of the new Section name is awaiting a decision by the WPA General Assembly.

Section members have been conducting innovative research in the context of Immunopsychiatry. They contributed a total of thirteen articles reflecting their research that were included in a Special Issue of the Journal of Affective Disorders Reports of which I had the privilege to be the guest editor.[1] Each of these articles refers to a different aspect of Immunopsychiatry. The subject topics cover a wide array of inflammatory pathways, related mechanisms of action including cellular, subcellular, structural, biomarkers, and axes of inflammation. Examples include identifying potential brain circuit-based biotypes for personalized treatment selection in mood disorders; translating individual-level brain circuit function into predictive markers for clinical practice and increasing evidence that pharmacogenomics can provide guidance for selection of medication(s) congruent with the pharmacogenomic profile of the individual patient thereby enabling the practice of Precision Psychiatry.[2] The immune system has emerged as a promising therapeutic target for certain sub-populations of subjects with depressive disorders.[3] Studies are actively exploring features of immunometabolism in depression as potential

predictors of antidepressant treatment outcomes, as well as proposed peripheral inflammatory biomarkers aimed at defining biotypes of unipolar and bipolar depression.[4]

Over the preceding decades extensive research efforts identified mechanisms of the inflammatory response in general, and, more recently, in psychiatric and neuropsychiatric disorders. Many blood-based biomarkers have been identified with emphasis on C-reactive protein (CRP) and cytokines. CRP has emerged as an inflammation biomarker that is elevated in different subtypes of depressive illness but also in other psychiatric disorders. It may also serve as a biomarker of treatment resistance, especially in conjunction with individuals who are carriers of specific single nucleotide polymorphisms (SNPs).[5] Amongst cytokines, Interleukin-6 (IL-6) is also associated with the metabolism of tryptophan and the kynurenine pathway. Specifically, activation of IL-6 leads to activation of the Interleukin-6-IDO pathway with associated pathophysiological consequences ultimately contributing to depressive illness and likely treatment resistance. With respect to the IDO pathway and tryptophan metabolism, tryptophan metabolites can predict response after cognitive behavioral therapy for depression and may be useful predictors of therapy response. Interleukin-17 (IL-17) also potentially plays a role in the pathogenesis of depression in the context of inflammation and specifically in association with suicidal behavior. Thus, IL-17 emerges as a potential mechanism relevant to neuroinflammation.[6,7]

Impressive examples of the complex interactions of the immune system, the nervous system and organ systems include the well-established Heart-Brain Axis, the Gut-Brain Axis, and, more recently the Lung-Brain Axis. The role of the vagus nerve has been addressed in publications by several section members. A well-functioning vagus nerve prevents long-lasting inflammatory states. Acetylcholine, the major neurotransmitter of the vagus nerve, is essential in the inhibition of production of inflammatory cytokines. Macrophages and other cytokine-producing cells have acetylcholine receptors, which, when activated, decrease cytokine synthesis. The gut-brain crosstalk, the role of the vagus nerve, and the microbiota-gut-brain axis in depression are new areas of endeavor. The vagus nerve is activated by several neurotransmitters produced by the gut microbiota, and it regulates the cholinergic anti-inflammatory pathway (CAIP), which attenuates inflammation and decreases intestinal permeability; both may be relevant in the inflammatory subtype of depression. The newly proposed Lung-Brain Axis discusses how common mechanisms may be involved in lung cancer and depression. Increasing evidence suggests that inflammation may be the key factor in this relationship, which includes activation of the indoleamine 2,3-dioxygenase (IDO) induced by increased interleukin (IL) 6, and consequently induced dysregulation of neurotransmission and suppression of lymphocyte functions.[8,9,10]

The complex interactions of the immune system with the central and peripheral nervous systems are further highlighted in a comprehensive review of the role mitochondria play in energy production, oxidative balance, cell survival/apoptosis, immune response, and inflammation. A possible role in affective disorders has fueled research on mitochondrial targets for novel treatments. Agents modulating inflammatory and mitochondrial mechanisms are expected to play a critical role in the design and implementation of an integrated treatment plan.[11]

Autoimmunity is increasingly recognized as a significant causative factor in conjunction with psychiatric disorders, especially those determined to be resistant to treatment. Novel mechanisms are being

identified linking psychiatric symptoms to the direct action of autoantibodies, e.g., autoantibodies aimed at structures in the central nervous system affecting key molecular components, as illustrated by the identification of autoantibodies targeting the N-methyl-D-aspartate receptor (NMDAR) in certain cases of encephalitis.[12]

The relationship between stress, especially early life stress, immune dysfunction and psychiatric disorders is now widely recognized. Early life stress has been associated with neurological, behavioral, chemical and endocrinological changes in adult life, and short- and long-term mental health disturbances, notably depression among others. Depressive symptoms and associated behavioral changes may be related to the NLRP3 inflammasome, a critical component of the innate immune system, which is being further explored as a potential diagnostic biomarker.[13]

In summary, these scientific advances hold great promise to further unravel the complex pathophysiology of psychiatric and neuropsychiatric disorders while enabling the development of more precise diagnostic tools and more effective treatment modalities aimed at practicing Precision Psychiatry. Immunopsychiatry has therefore the potential to become a clinically relevant subspecialty area in psychiatric practice, but it has yet to be widely recognized and adopted by the mental health community worldwide.

During the past triennium, our Section organized symposia at World Congresses of WPA, WPA co-sponsored congresses, and Thematic Conferences. Similar activities including Educational Workshops and Thematic Conferences with other sections will be organized in the new triennium.
Our goals include continuation of scientific advances and enabling clinicians, mental health providers and researchers to advance Immunopsychiatry and Precision Psychiatry worldwide.

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