DEVELOPMENT OF NOVEL PAIN MEDICATIONS AND THE VALLEY OF DEATH

The current opioid crisis underscores the need for pain medications that do not carry the risk of dependency and addiction and are not constrained by a narrow therapeutic index, all such properties being strikingly exhibited by opioids. To assess the landscape of the development of such pain medications, Hwang et al undertook a retrospective analysis of pain medications undergoing clinical trials between 2000 and 2015, a study published in the present issue of Mayo Clinic Proceedings. Drugs were broadly divided into two categories: new pain drugs (including drugs directed to novel biologic processes underlying their analgesic action and not approved by the US Food and Drug Administration); and reformulated pain drugs (including abuse-deterrent opioid formulations) representing derivatives of pain medications in current clinical use. The data demonstrate that there was a significant decrease in the proportion of new pain drugs (as indexed against all new drugs) beginning Phase 1 clinical trials over a 3-year period at the start and at the end of the time frame of this study, whereas this proportion remained relatively stable for new pain drugs entering Phase 2 or Phase 3 clinical trials. There was a marked attrition in new pain drugs successfully progressing to Phase 3 clinical trials, with only 11% of new drugs starting Phase 2 clinical trials advancing to Phase 3 clinical trials. New drugs failed to progress for the most part because of a lack of demonstrable efficacy. In contrast, over the time frame of this study, the number of reformulated (opioid and nonopioid) pain drugs starting Phase 1 trials increased, and by the end of this time frame of study, had outstripped new pain drugs beginning such studies. Based on their findings, Hwang et al emphasize a number of points that include the following considerations. First, reformulated pain drugs are commonly abuse-deterrent opioids, but the long-term efficacy and cost of this latter therapeutic strategy is currently uncertain. Second, new pain drug development is sponsored mainly by relatively smaller pharmaceutical companies, leading Hwang et al to suggest the need for the provision of incentives to such manufacturers by health care policymakers. Third, Hwang et al strongly emphasize the need to significantly enhance funding for basic research on the biology of pain. This call is firmly founded on innumerable examples in clinical practice wherein drug development proceeded from an understanding of the relevant biology and pathobiology. It should be noted, however, that the discovery of compounds effective in preclinical studies and the translation of such discoveries into novel therapies is a long, costly, and winnowing process. Only a fraction of such compounds successfully traverse what is called “the valley of death” in drug development. Hwang et al call attention to the fact that the development of novel pain medications is declining as
compared with all new drug development, a sobering finding especially in light of the current opioid crisis. Increasing basic research in the biology of pain and discovering new ways to interrupt the processes of pain would secure a pipeline of novel analgesic compounds, some of which, hopefully, would advance through clinical trials and become therapeutic realities.


STEERING BETWEEN THE SCYLLA AND CHARYBDIS OF CLOTTING AND BLEEDING IN CANCER
The risk for venous thromboembolism (VTE) is increased several-fold in patients with cancer, and such occurrence of VTE increases morbidity and mortality in this patient population. This risk of VTE is increased because of a prothrombotic milieu created by the presence of cancer (variably so depending upon the type of cancer); the prothrombotic effects of certain chemotherapies and other cancer-targeted therapies; the need for hospitalization and surgical procedures; patient-dependent factors (age, body mass index, other co-existing illnesses); patient debility and decreased mobility; and the use of central venous catheters. Therapies that decrease the risk of VTE in patients with cancer, however, may incur the risk of the opposite outcome, namely, bleeding, and one to which the cancer patient is already predisposed; an increased risk of bleeding may arise from the regional, systemic, and bone marrow effects of the underlying cancer as well as from the adverse effects of cancer-targeted procedures and therapies. The Scylla and Charybdis of thrombosis and bleeding may thus coexist in cancerous states. Direct oral anticoagulants (DOACs) represent a major therapeutic advance as they challenge the use of warfarin in certain clinical settings on such grounds as efficacy, safety profiles, relative ease of dosing, pharmacokinetic consistency, and the need for monitoring. Interest thus surrounds the use of DOACs in treating acute VTE in patients with cancer. In the present issue of Mayo Clinic Proceedings, the systematic review and network meta-analysis of Fuentes et al examine the relative efficacy of DOACs in treating VTE associated with cancer. Prior landmark studies established the superiority of low molecular weight hepwarin (dalteparin) over coumarins (warfarin) in cancer-associated VTE. Until recently, low molecular weight heparins, including dalteparin, have been broadly recommended as the preferred treatment in preventing the recurrence of VTE. Fuentes et al analyzed the results from 3 randomized controlled trials involving more than 1700 patients which assessed the efficacy and safety of DOACs as compared with dalteparin. In this analysis by Fuentes et al, the major treatment outcome was recurrent VTE, while the safety outcomes involved major bleeding and clinically relevant nonmajor bleeding (CRNMB). The essential findings of the analysis of Fuentes et al are that DOACs reduce the risk of recurrence of VTE as compared with dalteparin, with apixaban, among the DOACs, appearing most effective in such risk reduction. DOACs, as a class, however, increased the risk of major bleeding as compared with dalteparin, with a comparable occurrence in CRNMB in these two groups. As is commonly the case in clinical medicine, newer therapies bring clear benefits, but with certain attendant trade-offs, and in this case, DOACs significantly reduce the risk of VTE in patients with cancer, but with the trade-off of augmenting the risk of major bleeding.


ENDOTHELIAL BEHAVIOR IN POLYCYSTIC OVARY SYNDROME AND IN RESPONSE TO METFORMIN
In health, the entire endothelium is a sizable organ that approximates 1 kg in weight and
provides a surface area approaching that covered by a football field. This metabolically active cellular surface lining blood vessels produces vasodilators such as nitric oxide and prostacyclin, and other vasoactive species; fundamentally regulates vascular tone and reactivity; is antithrombotic and anti-inflammatory; senses and responds to signals in the circulation; and vitaly enables tissue perfusion. Endothelial integrity can be compromised by a plethora of insults (hypertension, smoking, hyperglycemia, hyperlipidemia, hyperuricemia, uremia, sepsis, among others), and the ensuing endothelial dysfunction largely reflects decreased bioavailability of nitric oxide. Endothelial dysfunction is not only a hallmark of existing clinical vascular disease, but endothelial dysfunction may be a harbinger of vascular disease that will subsequently develop. Endothelial dysfunction is thus of both diagnostic and prognostic significance, and its presence in diseases not conventionally considered as cardiovascular in nature may be of special interest. In this regard, the study by Heidari et al in the current issue of Mayo Clinic Proceedings provides novel insights regarding endothelial behavior in polycystic ovary syndrome (PCOS) and in response to metformin. PCOS, a relatively common endocrinopathy in women, is characterized by menstrual irregularity, hyperandrogenism, and cystic ovaries, but not by overt cardiovascular disease. Heidari et al assessed endothelial function by a method based on flow-mediated dilation. This method involves transient limb ischemia induced by the application of cuff pressure above systolic blood pressure, which when released, is accompanied by reactive hyperemia—the magnitude of the hyperemic response provides a measure of endothelial function. The device employed by Heidari et al in this study evaluates such responses in the index finger, ones that represent microvascular (as opposed to macrovascular) endothelial responses. Heidari et al found that approximately 36% of patients with PCOS in their study exhibited endothelial dysfunction. Interestingly, while metformin administered for 3 months did not exert an overall effect on endothelial function when all subjects were considered, metformin did improve endothelial function in those subjects with baseline endothelial dysfunction. These effects of metformin appeared independent of alterations in glucose metabolism, insulin resistance, level of androgens, and lipid profiles. The findings of Heidari et al raise several salient considerations. First, subjects with endothelial dysfunction as compared with those with normal endothelial function exhibited comparable systemic blood pressure, fasting plasma glucose concentrations, and plasma levels of insulin and c-peptide; this raises the possibility that the mechanisms underlying endothelial dysfunction in PCOS may be upstream of or relatively independent of these hemodynamic and metabolic processes in PCOS, or may be driven by yet-to-be-defined pathobiologic processes in PCOS. Second, the improvement in endothelial dysfunction by metformin was independent of metabolic effects, leading to the plausible speculation by the authors that other effects of metformin, including its increasingly recognized anti-senescence effects, may be relevant. Finally, while obesity, insulin resistance, and sleep apnea occur more frequently in patients with PCOS and are conditions that predispose to cardiovascular diseases, the true risk for cardiovascular diseases in PCOS remains uncertain. Heidari et al suggest that evaluating endothelial behavior may aid in defining the relative risk for such complications and in identifying those who would most likely benefit from metformin therapy.


Karl A. Nath, MBChB
Editor-in-Chief