Preface

Comments from Irwin Goldstein MD, Meeting Co-Chair

An international, multi-disciplinary meeting was held in Puerto Rico January 21 to 23, 1999, to discuss in consensus format the topic of 'Alpha Blockade in Sexual Function'. The faculty included researchers and clinicians with significant experience in the field of alpha blockers in sexual medicine. The conference faculty in attendance consisted of: Karl-Erik Andersson PhD, John Bancroft MD, David Ferguson PhD, MD, François Giuliano MD, Tom Lue MD, Alvaro Morales MD, Inigo Saenz de Tejada MD, Abdul Traish PhD, Gorm Wagner MD, PhD and Michael G. Wyllie PhD. The meeting co-chairs were Harin Padma-Nathan, MD, Raymond Rosen PhD and myself.

The major goals of this meeting were as follows:

1. To review existing basic science data concerning: (a) the role of adrenergic activity locally and centrally in erectile function; (b) the functional activity of alpha-1 and -2 adrenergic receptors in corpus cavernosum tissue relating to identification, characterization, subtypes; (c) agonist/antagonist and hormonal regulation; and (d) the concept of functional antagonism of the alpha adrenergic signaling pathway and its modulation by non-adrenergic, non-cholinergic neurotransmitters and by vasoactive agents.

2. To translate the basic science research of alpha-adrenergic activity into effective strategies for the management of men with erectile dysfunction by developing an integrated model of the physiological mechanisms regulating penile erection. The intent is that this model be used as a basis for evaluating current pathophysiological theories and pharmacological interventions. Alpha adrenergic components of the model will be identified, based upon current research data.

3. To review the clinical pharmacology data and experience with alpha adrenergic blockade in erectile dysfunction with such agents as delequamine, yohimbine, doxazosin and abanoquil as well as the new safety, metabolism, pharmacokinetic and clinical data on oral phentolamine in the treatment of erectile dysfunction. The implications of this data of alpha blockade in the clinical treatment of erectile disorders will be considered in detail. Implications for further clinical research will also be reviewed.

4. To disseminate the major findings of the meeting.

Prior to the meeting, all participating faculty received a package of relevant background publications and reprints on the topic of alpha blockers and sexual function. Meeting highlights included multiple basic science presentations on alpha-adrenergic activity in erectile function, followed by clinical experience presentations with six different alpha blockers and their future implications in the treatment of erectile dysfunction. All presentations were followed by lively discussions and, at the end of each session, a general interactive debate ensued. The educational event was highly instructional, informational and energetic with a high level of discourse.

The purpose of this supplement entitled ‘Alpha Blockade in Sexual Function’ is to publish the proceedings of the meeting. Over the past decade the primary focus of research and clinical attention on the physiological mechanisms of penile erection has been the nitric oxide pathway for initiating corporal smooth muscle relaxation. However, little attention has been given to the physiologically and clinically significant contractile pathway for initiating corporal smooth muscle contraction and penile detumescence. The meeting emphasized that the true concept concerning global physiologic control of corporal smooth muscle contractility involves both contractile and relaxatory pathways. The modulation of this balance between contraction and relaxation which regulates erectile function needs to be better defined. The proceedings of this meeting identified key areas of consensus, as well as critical gaps in the existing scientific knowledge base concerning alpha blockers and erectile function.

Comments from Harin Padma-Nathan MD, Meeting Co-Chair

The advent of safe and effective oral agents for the treatment of erectile dysfunction has revolutionized the office management of this highly prevalent disorder. For the first time, large numbers of men suffering from sexual dysfunction are presenting for medical assessment and treatment. At the same time, practice patterns have evolved rapidly from highly specialized (i.e., urology, sex therapy) to primary care treatment.

First line therapies for erectile dysfunction presently focus on the use of oral pharmacological agents. Although attention has centered recently on
the use of a phospodiesterase inhibitor (sildenafil) as the first line drug of choice, other drug classes may play a significant role in the future. In particular, the class of alpha blocking agents deserves consideration. This class of drugs has a long history of use in the treatment of common medical disorders (e.g. hypertension, benign prostatic hypertrophy), and has recently been shown to be safe and effective in the treatment of erectile dysfunction.

Despite the fact that there is a large body of information concerning alpha blockade in erectile function, this research is less familiar to physicians and the public. A greater understanding of the specific role of oral alpha blocking drugs in erectile dysfunction is needed.

This supplement reviews the scientific and clinical basis of alpha blockade in the first-line treatment of erectile dysfunction. The authors are internationally recognized experts in this field and include both clinical and basic science researchers. Ultimately it is hoped that this body of scientific material will be translated into effective strategies for the management of patients with erectile dysfunction through development of an integrated model of the control of penile erection (‘The Balance of Forces’).

**Comments from Raymond C. Rosen PhD, Meeting Co-Chair**

Male erectile dysfunction is a ‘hot’ topic of increasing concern to primary care practitioners, basic and clinical scientists, epidemiologists and health economists, and the pharmaceutical industry. Since the approval of sildenafil in 1998 as the first orally active agent for the treatment of male erectile dysfunction, a number of other drug types and classes have come under intense investigation. Among these, the class of alpha blocking agents warrants particular attention given the long history of association between these drugs and their effects on sexual functioning in animals and humans. Historically, alpha blocking agents have been used in the treatment of erectile dysfunction prior to the advent of phosphodiesterase inhibitors. However, while physicians are generally familiar with the use of alpha blockers in the treatment of hypertension and benign prostatic hyperplasia (BPH), they are less aware of the role these agents may play in erectile function.

This conference succeeded admirably in bringing together, for the first time, a distinguished group of clinical and basic science investigators, all of whom have conducted significant research on the topic of alpha blockers and male sexual function. Why the major interest in alpha blockers at this time? First, as illustrated by several of the basic science papers at this meeting, a ‘balance of forces’ concept is necessary to explain the interactive effects of excitatory (relaxant) and inhibitory (contractile) mechanisms in the control of penile corporal smooth muscle. While the role of nitric oxide and its second messenger, cGMP, is well established as a primary factor in smooth muscle relaxation, the role of adrenergic mechanisms in the contractile process is less well recognized. Hopefully, the first several papers in this collection will go a long way towards correcting this imbalance. Second, there is an extensive literature on the pro-erectile effects of alpha blockers in both humans and other mammals. Yohimbine, an alpha-2 antagonist, has been widely studied in animals, and has been used clinically for the past half century, despite a lack of well-controlled outcome research. Alpha-1 antagonists, such as doxazosin, which are commonly used in the treatment of BPH or hypertension, have been observed to be associated with mildly positive effects on male sexual function. Other, alpha-1 and alpha-2 antagonists have similarly demonstrated varying degrees of pro-erectile activity, as illustrated by several papers in the second session. Finally, the issue of cardiovascular safety has become a major concern in the treatment of erectile dysfunction. Alpha blockers have a long history of use in cardiovascular disease, and may offer unique safety advantages in the treatment of patients with ED and comorbid cardiac conditions.

Some major themes and research issues of the present conference are worth notice:

1. Several receptor subtypes have been identified within the alpha adrenergic system, each of which may have discrete effects on male sexual function. Individual papers at this conference have suggested that pre-synaptic, alpha-2 receptors are involved in the central control of erection, whereas post-synaptic alpha-1 and alpha-2 receptors are involved in peripheral relaxant and contractile effects on corporal smooth muscle. As a further complication, it has been suggested that there may be species-specific differences in the relative roles of certain receptor subtypes. Clearly, further research is needed on this issue.

2. Although the independent effects of alpha-1 and alpha-2 stimulation and blockade have been described in several papers, relatively little attention has been paid to the combined or interactive effects of alpha-1 and alpha-2 blockade. Based on the clinical findings reported with oral phentolamine, it appears that a combination of alpha-1 and alpha-2 blockade may offer certain advantages, although further basic science research is needed to elucidate the specific mechanisms involved.

3. Important interactions may also occur with other neurotransmitter systems, particularly the nitricergic and cholinergic systems. Given the pervasive distribution of alpha adrenergic receptors and extensive co-localization with other neurotransmitters,
considerable potential exists for interaction effects at either pre-synaptic or post-synaptic levels. These findings suggest that combination drugs, or drugs which affect multiple transmitter systems, may offer unique advantages in the treatment of erectile dysfunction.

(4) Although pro-erectile effects have been demonstrated with a growing number of alpha blockers (yohimbine, delequamine, doxazosin, abanoquil, phentolamine), it is unclear at this time whether a single mechanism of action underlies this effect. Do all alpha blockers promote erection via direct inhibition of corporal smooth muscle contractile mechanisms? Do any of these agents enhance central excitation mechanisms? At a local level, does alpha-1a or -1b blockade enhance the release of cGMP or cAMP? Additionally, it is unclear to what degree each of these agents require concurrent sexual stimulation (central or peripheral) to be effective.

(5) Assuming that sympathetic inhibition is an important component, which patient groups might be most responsive to the pro-erectile effects of alpha blockade? Theoretically, patients with elevated sympathetic tone are at increased risk for ED, and may be ideal candidates for first-line therapy with an alpha blocking agent. This hypothesis has not been evaluated systematically in pre-selected patient sub-groups. Similarly, human studies have yet to demonstrate an association between improved erection and independent markers of peripheral sympathetic activity (e.g. NE levels).

(6) Given the current emphasis on cardiovascular safety in the office management of erectile dysfunction, it is important to carefully evaluate the cardiovascular risk profile of oral phentolamine and other alpha blockers for ED. Based upon the clinical trial data presented at this meeting, phentolamine appears to have an excellent overall safety profile. However, further studies are clearly needed of potential interaction effects with nitrates, antihypertensives and other cardiovascular agents. Additionally, the safety of phentolamine in specific patient groups (e.g. post-MI patients, patients on multiple antihypertensives) should be further evaluated.

(7) Finally, further studies are needed of the efficacy of oral phentolamine (and other alpha blockers) in patients with more severe degrees of erectile dysfunction. Major limitations of the clinical trial data presented at this meeting were the selection of patients with milder degrees of ED and the use of relatively brief treatment periods. Patients with a broader range of severity should be followed for longer periods of time in order to evaluate the viability of oral phentolamine as a first line agent for erectile dysfunction.

In conclusion, this conference provided a unique overview of basic science and clinical data on the effects of alpha blockers in erectile function. Clearly, the “balance of forces” concept has much to offer for both clinicians and basic scientists in this rapidly-evolving field. A number of critical research issues were identified during the course of the meeting, which will hopefully serve as a stimulus for further studies in the years to come. It is also hoped that the presentation of clinical data will lead to greater availability of treatment options in the future, and to more individualized therapy of the male patient with erectile dysfunction.