Cardiovascular Endocrinology: Introduction

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I. Introduction

It has been an Endocrine Society tradition for the President to select a theme for his/her year in tenure. The theme Cardiovascular Endocrinology was selected (by J.D.B.) because endocrinologists have made so many fundamental basic and clinical contributions to this field. Yet, to some extent, these contributions are under-recognized. The 2003 cardiovascular endocrinology theme is being emphasized in a number of ways. The Annual Meeting in June features an increased number of presentations in this area (plenary lectures, symposia, meet the professor sessions, and workshops), a cardiovascular dinner open to all, free assessment of cardiovascular risk profiles, and a fun run/walk. The Society is also sponsoring a “Hot Topics” 3½-day meeting on cardiovascular risk profiles, and a fun run/walk. The Society members are giving presentations on management of lipid disorders and hypertension to groups of physicians in practice at a number of locations. The Hormone Foundation, our public outreach arm, is planning materials for availability to the public to highlight the metabolic syndrome and its associated abnormalities (discussed below) for dissemination through lectures, the Foundation’s web site, and printed materials.

There is also emphasis of the theme by publications in The Society’s journals. We are delighted that Endocrine Reviews has devoted this issue of its journal to this theme. The Journal of Clinical Endocrinology & Metabolism has also dedicated an issue to the theme. Endocrinology is featuring articles on obesity, renin angiotensin-system, and primary aldosteronism. Molecular Endocrinology is targeting articles related to hormone action and the cardiovascular system that use genomic and proteomic approaches to address mechanisms, analyze gene and protein expression profiles, and identify new candidate genes or proteins. All four journals are also publishing other papers related to the theme in other issues.

In our roles as President (J.D.B.), Annual Meeting Theme Chair (W.F.Y.), and Chair of the Hot Topics Meeting (P.W.), we use this opportunity to introduce the theme of Cardiovascular Endocrinology. Endocrinologists have made great contributions to understanding the function of the cardiovascular system in health and disease. Cardiovascular tissues are endocrine organs, and stimuli that affect the cardiovascular-system work through hormone receptors. Many of these hormone-signaling systems are so interwoven and interconnected that, in many cases, the components are hard to separate.

In this introduction, we provide a brief overview of the relations of the endocrine system to the cardiovascular system, and the role of the endocrinologist in management of disorders that affect the cardiovascular system.

II. Endocrine Signals and the Cardiovascular System

The cardiovascular system responds to multiple endocrine signals, and there are strong parallels between the mechanisms of endocrine and other types of signals that influence the function of the cardiovascular system (nutritional signals, nerve inputs, etc.). Endocrine signals that influence the cardiovascular system can be divided largely into two types according to whether they are mediated by nuclear receptors (including cholesterol and fatty acid metabolites, steroids, and thyroid hormones) or cell surface receptors that work by initiating second messenger signaling cascades (including peptide hormones, cytokines, and neurotransmitters). We discuss below the roles of nuclear and cell surface receptors separately. However, in reality, the actions of both types of signal overlap extensively and are significantly integrated.

III. Nuclear Receptors

The nuclear receptors are a large family of conditional transcription factors that consist of single polypeptide chains with separable domains that mediate ligand binding, transactivation and transrepression, DNA binding, and interactions with other coregulatory proteins (1–3). The family may have first evolved as nutritional sensors, because it includes...
receptors that transduce signals of fatty acid and cholesterol metabolites, vitamins, and bile acid breakdown products; however, these receptors also acquired more classical endocrine signaling capacity during evolution, as they transduce actions of the classic steroid and thyroid hormones, among others. The nuclear receptor family has extensive and overlapping effects on the cardiovascular system, including roles in atherosclerotic plaque formation, cholesterol and lipid metabolism, heart rate, heart function and contractility, and vascular response (Table 1). Nuclear receptors also regulate inflammatory responses, which are emerging as a key contributor in the incidence of cardiovascular disease (4). Some of the complexity of nuclear receptor signaling in cardiovascular disease is illustrated in Fig. 1, which highlights direct and indirect effects of nuclear receptors on atherosclerotic plaque formation.

**TABLE 1. Nuclear receptors in cardiovascular disease**

| Reverse cholesterol transport | PPARγ, LXRα |
| Lipoprotein levels | PPARs, LXRs, FXRs, SHP, TRs, ER, AR, VDR |
| Atherogenic response | PPARs, LXR, RORα, RXR, VDR, ER, AR |
| Cardiac fibrosis | MR |
| Blood pressure | MR, GR, ER |
| Obesity/metabolic syndrome | PPARs, TR, GR, RARs, RXR |
| Vascular tone | ER, AR, MR |
| Arrhythmia | TR |
| Cardiac myopathy | PPARs, TR |

SHP, Short heterodimer partner; AR, androgen receptor; ROR, retinoid orphan receptor; RXR, retinoid X receptor; RAR, retinoic acid receptor.

Much attention has been directed toward the role of the three peroxisomal proliferator-activated receptors (PPARs), whose natural ligands are fatty acids and eicosanoids (5–7). The family has widespread effects on lipid and lipoprotein metabolism and glucose homeostasis and also influences proliferation, differentiation, and apoptosis. PPARα is expressed in liver, muscle, kidney, and heart and is involved in β-oxidative degradation of fatty acids. It mediates actions of hypolipidemic fibrate drugs on plasma lipoprotein metabolism. Down-regulation of PPARα is implicated in development of pathological cardiac hypertrophy (8). PPARγ is expressed in intestine and adipose tissue and regulates adipocyte differentiation and lipid storage. It mediates actions of ligands of the glitazone class that are used to treat diabetes and hypertension. Unfortunately, the glitazones can also lead to obesity, and a search is currently on for dissociated ligands, for which preliminary data suggest might be possible (9). PPARβ/δ is expressed in many tissues, and this receptor may play a role in adipogenesis. In addition, PPARs work in reverse cholesterol transport and inhibit inflammatory response genes in the immune system and vascular wall. This finding points toward possible uses in treatments of inflammatory diseases such as atherosclerosis.

The two liver X receptors (LXRs) are activated by oxysterols and have a role in hepatic bile homeostasis (10, 11). LXRs stimulate transcription of the ATP-binding cassette 1 (ABCA1) transporter gene in the macrophage. This transporter removes cholesterol from foam cells, transferring it to high-density lipoproteins (HDL) and thereby promoting reverse cholesterol transport to the liver. Thus, PPARγ and LXRs synergize in reverse cholesterol transport (Fig. 2). For this reason, there is an intense effort to develop ligands that might be used to stimulate reverse cholesterol transport and remove cholesterol from arterial plaques. The LXRs and their ligands are also ligand-dependent inhibitors of inflammatory gene expression in macrophages and aortas of atherosclerotic mice, pointing to a dual and reciprocal role in lipid metabolism and inflammatory responses (12).
The farnesyl X receptors (FXRs) protect the liver from accumulation of toxic bile acids and xenobiotics by inducing cholesterol 7α-hydroxylase and stimulating excretion and transport of bile acids (10). Ligands that act through this receptor may have clinical utility.

The classic steroid receptors also influence cardiovascular disease. Aldosterone is a well known cardiovascular risk hormone whose actions are mediated through the mineralocorticoid receptor (MR). Aldosterone was discovered 50 yr ago, and its role in sodium and potassium homeostasis has been studied in detail. The syndrome of primary aldosteronism, whereby constitutive production of aldosterone due to adrenal hyperplasia or an adrenal adenoma, is also well understood. New interest in this hormone has emerged for two major reasons (13). First, aldosterone has deleterious effects on the heart (and on the kidneys and vasculature) to cause cardiac fibrosis that are independent of its blood-pressure-elevating activities. Second, primary aldosteronism is a much more common cause of hypertension than was previously realized, accounting for as much as 5–10% of cases of so-called essential hypertension (14–16). Glucocorticoid receptors (GRs) have extensive effects in the metabolic syndrome (17) but are also classic antiinflammatory hormones (18). The increasing realization of the importance of inflammatory response in cardiovascular disease points toward possible roles for dissociated glucocorticoids in medical therapy.

Other steroid receptors play key roles in cardiovascular disease. Receptors for androgens (ARs) mediate actions of testosterone and dihydrotestosterone and have extensive effects on the cardiovascular system. An article by Drs. Peter Y. Liu, Alison K. Death, and David J. Handelsman in this issue of Endocrine Reviews discusses androgens in relation to vascular biology, coronary artery disease, hypertension, cardiac hypertrophy, cerebrovascular disease, peripheral arterial disease, and other aspects of cardiovascular biology. Estrogen receptors (ERs) mediate diverse actions on the cardiovascular system (19). These actions involve influences on the vasculature, lipoprotein metabolism, and other systems. Interestingly, some of these estrogen effects on the vasculature may not involve classic effects on ERs on gene transcription, but may instead involve nonclassical effect of estrogens at the cell membrane. The article by Dr. Peter Y. Liu et al. in this issue of Endocrine Reviews focuses mostly on androgens but also discusses the relation of estrogens to cardiovascular disease. These authors point out that, until recently, it was thought that estrogen replacement in postmenopausal women would prevent cardiovascular complications, but recent prospective trials have not supported this notion (20). For example, in previous case-control studies, selective recruiting of women into the trial who are more likely to follow a healthier lifestyle than in the general population may have given false reassurance of the benefits of estrogens. Moreover, the previous dominance of the estrogen protection hypothesis overlooked evidence that there is no break-point in female cardiovascular risk at the expected age of menopause, a key prediction of this hypothesis. Nevertheless, the cardiovascular effects of this class of hormones cannot be denied, and in the future a regimen may be developed in which there may be potential beneficial effects of estrogens.

Thyroid hormone receptors (TRs) regulate diverse aspects of physiology related to the cardiovascular system (21–24). They have profound and direct effects on the heart. They can increase the force of cardiac contractility and are being tested for their ability to treat heart failure. TR activation increases the rate of contraction of the heart and, in excess, can result in atrial arrhythmias. TRs have profound effects on lipid and lipoprotein metabolism. TR activation stimulates cholesterol synthesis, promotes cholesterol breakdown, and elevates low-density lipoprotein (LDL) receptors. Despite the increased synthesis of cholesterol, the net effect is to decrease plasma levels of LDL.

It is likely that many other nuclear receptors play roles in the normal function of the cardiovascular system and in cardiovascular disease. For example, retinoic acid receptors (RARs) inhibit vascular smooth muscle cell growth (25) and play crucial roles in heart development (26). The retinoid orphan receptor-α (RAR-α) gene affects susceptibility to atherosclerosis (27). Rapid advancements in pharmacology of the nuclear receptor family suggest that it will be possible to devise new treatments for cardiovascular disease based on modulation of the actions of many nuclear receptors.

FIG. 2. Nuclear receptor influences on reverse cholesterol transport in the macrophage/foam cell. PPARγ enhances expression of CD36, which promotes uptake of oxidized LDL cholesterol into macrophages, and of LXRα that induces expression of ABCA1, which enhances transport of cholesterol out of the cell.
IV. Second Messenger Signaling Systems

The function of the cardiovascular system is also extensively regulated by hormones that bind to surface receptors (26, 28, 29). Hormone binding to surface receptors triggers complex chains of integrated intracellular second messenger pathways (including phosphorylation cascades, generation of cAMP and cGMP, polyinositol, Ca\(^{2+}\) fluxes, and nitric oxide) with diverse effects.

One of the most extensively studied signals that influences the cardiovascular system and works through membrane-bound receptors is that of the catecholamines, whose actions are mediated through \(\alpha\)- and \(\beta\)-adrenergic and dopamine receptors (30, 31). The catecholamine system regulates vascular tone and has multiple complex actions on the heart. The importance of the system in cardiovascular endocrinology is underscored by the extensive use of drugs that target each of the receptors. \(\beta\)-Adrenergic blockers are in widespread use as treatments for hypertension, angina pectoris, and tachycardia. These drugs work by blocking catecholamine binding to \(\beta\)-adrenergic receptor sites. In addition, \(\beta\)-adrenergic antagonists are used to treat asthma, and \(\alpha\)-adrenergic antagonists are also used to treat certain forms of hypertension, including catecholamine-secreting pheochromocytomas and paragangliomas (32).

The renin-angiotensin system has been intensively studied by endocrinologists and has its primary effects on the cardiovascular system (33, 34). Recently recognized components of the renin-angiotensin system and their potential roles in cardiovascular and renal regulation are reviewed in an article by Drs. Robert M. Carey and Helmy M. Siragy in this issue of *Endocrine Reviews*. Renin of renal origin is released into the circulation where it acts to generate angiotensin I, a decapeptide. Angiotensin converting enzyme then generates the octapeptide angiotensin II from angiotensin I. Angiotensin II has multiple actions, including the stimulation of vasoconstriction, vascular hypertrophy, and the release of aldosterone (discussed above). Other peptides active on the cardiovascular system can be generated from angiotensinogen, and their roles are currently being defined. In addition to the circulating renin-angiotensin system, components of the system are expressed in local tissues, where they exhibit important actions. The renin-angiotensin system is also involved in the pathogenesis of renovascular hypertension, another treatable and potentially curable form of hypertension.

The importance of the renin-angiotensin system in disease is underscored by the widespread use of blockers of the system (35–37). These blockers can inhibit angiotensin converting enzyme or the angiotensin II receptor. Thus, these blockers are used as one of the best means to treat hypertension. They help to prevent the progression of renal disease in the diabetic and in other states, and are important for treatment of heart failure.

Insulin receptors have extensive effects on the cardiovascular system, including regulation of vascular resistance. Resistance to insulin is a central component of the metabolic syndrome and is of vast medical importance. The metabolic syndrome also includes (to varying degrees) diabetes mellitus, dyslipidemia, hypertension, visceral obesity, increased thrombogenicity, microalbuminuria, and polycystic ovary syndrome. That polycystic ovary syndrome may adversely affect or accelerate development of an adverse cardiovascular risk profile, and even of subclinical signs of atherosclerosis, is discussed in an article in this issue of *Endocrine Reviews* by Dr. Richard S. Legro. However, Dr. Legro also emphasizes that it may be premature to assign an association between polycystic ovary and cardiovascular disease. In another article in this issue, Drs. J. M. Fernández-Real and Wifredo Ricart discuss interrelationships between insulin resistance and atherosclerosis, and the similarities between these two processes as inflammatory conditions, with similar pathophysiological mechanisms due to actions of certain proinflammatory cytokines. In fact, many additional hormones influence various inflammatory cytokines (4) with consequent influences on inflammation in arterial walls, blood pressure, vascular hypertrophy, and proliferation and release of other hormones. For example, tumor necrosis factor can induce insulin resistance and is regulated by multiple hormones.

Atrial peptides are produced in the heart and, to a lesser extent, in other tissues (38). These include atrial natriuretic peptide and brain natriuretic peptide. In fact, the cardiac atria synthesize more natriuretic peptides than most other proteins. Receptors for these peptides are present in the heart and peripheral vessels, and they have vasodilatory actions, tend to block the renin-angiotensin system, increase the glomerular filtration rate, and enhance sodium excretion. Because they are elevated in heart failure, measurements of plasma levels of the peptides are one of the more important ways to diagnose and monitor heart failure. The use of cardiac hormones as diagnostic tools in heart failure is discussed by Dr. Heikki Ruskoaho in an article in this issue of *Endocrine Reviews*. Brain natriuretic peptide is now approved by the Food and Drug Administration for treatment of heart failure.

GH has extensive effects on the cardiovascular system. In an article in this issue of *Endocrine Reviews*, Dr. R. N. Clayton reviews these effects, including the facts that in acromegaly with GH excess there is an increased prevalence of cardiovascular mortality risk factors including hypertension, type 2 diabetes mellitus, dyslipidemia, abdominal adiposity, insulin resistance, endothelial dysfunction, and other specific effects on the heart and cardiac function.

Calcium ion levels in the circulation are regulated by PTH that acts on the cell surface and by vitamin D, whose metabolite acts through nuclear receptors (39). Calcium ion levels in various cellular compartments are also regulated extensively by hormones that act on the cell surface. Calcium ions are involved in regulating blood pressure and numerous aspects of vascular biology. They are also deposited in atherosclerotic plaques, a process under hormonal control.

In addition to signaling events, the cell membrane also plays key roles in regulation of import and export of cholesterol into different cells and tissues. The dual role of PPAR\(\gamma\) and LXR\(\alpha\) in regulation of reverse cholesterol transport via regulation of CD36 and ABCA1 in macrophages/fus cells has been discussed above. Cholesterol is also a precursor for synthesis of steroid hormones, and steroidalogenic tissues have adopted a variety of different strategies to maintain adequate supplies of cholesterol, including import.
from lipoproteins, storage, and de novo synthesis. The mechanism of selective lipid uptake into steroidogenic tissues is discussed in an article in this issue of Endocrine Reviews by Drs. Attilio Rigotti, Helena E. Miettinen, and Monty Krieger. Steroidogenic tissues express high levels of a class B, type I scavenger receptor (SR-BI) that mediates selective lipid uptake. The liver also expresses SR-BI, where it plays a role in cholesterol import for biliary secretion. Analysis of genetically engineered mouse knockout models indicates that SR-BI protects against atherosclerosis. Thus, it may be useful to consider SR-BI (and, indeed, all of the proteins that are involved in cholesterol transport mechanisms) as a target for therapies in humans.

V. Clinical Endocrinology

Many aspects of clinical endocrinology focus on the cardiovascular system.

A. Hypertension

Hypertension is so common that it ordinarily falls into the realm of the generalist. Most hypertension is “essential,” meaning that the true cause has not been determined. However, there is increasing information about the mechanisms for hypertension, such that the proportion of patients that fall into the “essential” group is diminishing. It is commonly advantageous to identify the cause of hypertension, because sometimes it can be cured or greatly ameliorated through specific approaches. A number of hormonal disorders can cause hypertension (Table 2). The high incidence of primary aldosteronism is mentioned above. Unlike thinking in the past, it is now known that in most diagnosed patients the serum potassium level is in the normal range. Diagnosis of primary aldosteronism can result in either surgical cure of the hypertension or targeted pharmacotherapy. Patients with an aldosterone-producing adenoma may be treated with unilateral laparoscopic adrenalectomy. Patients with bilateral idiopathic hyperplasia are treated medically, ordinarily using a specific MR blocker. Realization of the need for surgical cure or MR blockade will be increasing with the increased age of the population. Thus, it will be insufficient just to treat the blood pressure.

Hypertension due to a pheochromocytoma is much more rare (estimated incidence 1.55–8 per million persons per year) than that due to primary aldosteronism (40, 41). It is important to suspect, confirm, localize, and resect pheochromocytomas because: 1) the associated hypertension is curable with surgical removal of the tumor, 2) of the risk of a lethal paroxysm, and 3) at least 10% of the tumors are malignant. Diagnosis is especially important because the hypertension may be most refractory to therapy, and, rarely, if a tumor is present, it may become malignant.

Renovascular hypertension is another curable form whose incidence is increasing with the increased age of the population (42, 43). Surgical therapy or percutaneous transluminal renal artery angioplasty can be curative, and specific therapy with blockade of the renin angiotensin system is, in most cases, beneficial.

Table 2. Endocrine causes of hypertension

<table>
<thead>
<tr>
<th>Drug Action</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal-related</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>Hyperdeoxycorticosteronism</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Adrenal-dependent</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Primary cortisol resistance</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>Renin-related</td>
</tr>
<tr>
<td>Renin-secreting tumor</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>Perirenal hematoma</td>
<td>Coarctation of the aorta</td>
</tr>
</tbody>
</table>

The endocrinologist is uniquely skilled at diagnosing these various causes of hypertension. Whereas the means for diagnosing these conditions has improved greatly in recent years, the tests are not always simple, and multiple tests are sometimes required to make a diagnosis.

B. Metabolic syndrome

As discussed above, the metabolic syndrome, with elements of abdominal obesity, insulin resistance, hypertension, dyslipidemia, and glucose intolerance (or type 2 diabetes mellitus), is increasingly recognized as a syndrome that should be treated as such (44). Current treatments involve attacking the individual components, although newer pharmaceuticals such as the thiazolidinediones affect more than one component simultaneously.

C. Obesity

Obesity is increasingly recognized as a pandemic of major proportions and a disorder that is life threatening and not just a cosmetic problem (45). Endocrinologists are among those currently making great strides to determine the mechanisms for obesity, and a number of specific mechanisms have been identified. As these are better defined, the information will lead to improved therapies. Also, a number of specific therapies are in development. It is also important to note that obesity can signify endocrine disease, as is seen
with hypothyroidism and Cushing’s syndrome. The clinician must be aware of these in approaching the patient with obesity.

**D. Dyslipidemia**

Lipid disorders contribute significantly to atherosclerosis. Gradually, management has shifted from total cholesterol to LDL and HDL and onto the additional consideration of other atherogenic species such as lipoprotein (a), homocysteine, and C-reactive protein, reflecting thrombogenic and inflammatory influences on the atherosclerotic processes. Furthermore, the upper limit of tolerability for LDL levels has crept down, such that a much higher proportion of patients have abnormal levels (46, 47). There is also more recent awareness that triglycerides comprise a risk factor for atherosclerosis that is independent of their effects on LDL or HDL (48). This is especially true for the diabetic patient (48).

Despite advances in means to treat dyslipidemia, treatment is inadequate in many cases, and most patients are not even screened for factors other than total cholesterol, LDL, HDL, and triglycerides. The statins that block cholesterol synthesis and appear to have additional antiinflammatory actions related to the atherogenic processes provide limited effects (49). Thus, increasingly, patients will be placed on multiple drug regimens. Whereas management of dyslipidemia by necessity will be placed predominately in the hands of primary-care physicians, the endocrinologist can play a specific role with patients that are difficult to control with standard regimens and that have unusual phenotypes. As with obesity, it is also remembered that hypothyroidism itself can result in elevations in LDL (21, 22). Cushing’s syndrome can also be associated with lipid abnormalities, and clinicians need to look for these conditions when appropriate (17).

**E. Thyroid disease**

Both hypothyroidism and hyperthyroidism have deleterious effects on the cardiovascular system (21–23, 50, 51). In hypothyroidism, there can be elevations of plasma levels of LDL, hypertension, and poor cardiac contractility leading to exacerbation of heart failure. Hyperthyroidism can lead to hypertension and several cardiac abnormalities. It can precipitate atrial arrhythmias, including atrial fibrillation. It can precipitate or exacerbate angina pectoris and possibly precipitate myocardial infarction. Hyperthyroidism can also lead to heart failure.

Thus, for these and other reasons, management of these disorders is important. In addition, up to 15% of women over the age of 60 have subclinical hypothyroidism, defined as abnormally elevated plasma thyroid-stimulating hormone levels with normal T₄ levels (23, 52). Although the literature is controversial, some studies suggest that this condition leads to elevations of LDL (53), and most endocrinologists feel that these conditions need to be treated as well, especially if there is evidence for dyslipidemia. Furthermore, subclinical hyperthyroidism, defined as a suppressed plasma level of thyroid-stimulating hormone and normal plasma T₄ levels may be associated with an increased incidence of atrial fibrillation (51). The endocrinologist can play a role in managing these disorders. Whereas in routine cases management of hypothyroidism is relatively straightforward, in many cases the management is more complex. This occurs, for example, in the elderly in whom replacement therapy must be initiated gradually and in patients with subclinical disease for which the criteria for initiation of therapy are less straightforward. Management of hyperthyroidism is more complex. With overt disease, there is the choice between medical therapy vs. radioactive iodine or surgery. Therapy in patients with heart failure or severe atherosclerosis is more complex. Most patients with subclinical disease will not progress to overt hyperthyroidism, and the criteria for initiation of therapy are more complex. The endocrinologist can serve a special role in these cases.

**F. Cushing’s syndrome**

The overt form of Cushing’s syndrome is easy to recognize, although one of us (J.D.B.) remembers as a medical student the missed diagnosis of Cushing’s disease as a presentation of malignant hypertension. Nevertheless, more and more we are diagnosing this condition at early stages in which the clinical presentation is more subtle (54). Almost all patients with spontaneous Cushing’s syndrome have hypertension (55), and, as stated above, these patients may also be obese. Although the means to diagnose and treat this disorder have improved greatly in recent years, the diagnosis of mild Cushing’s syndrome remains one of the most difficult diagnostic tasks for the clinical endocrinologist. The endocrinologist can be a valuable resource in sorting out the myriad of clues to diagnose the syndrome and determine the localization of the abnormally functioning tissue (adrenal, pituitary, ectopic).

**G. Diabetes and cardiovascular disease**

Cardiovascular disease is particularly prevalent in the diabetic patient (48, 55). In these patients, recent studies have indicated that there should be increased stringency in regulating the blood pressure and lipoprotein levels. Furthermore, blockers of the renin-angiotensin system have proved to be particularly helpful in preventing the progression of renal disease. Endocrinologists have traditionally been involved in treatment of diabetes and in consultation with other physicians regarding treatment. Given the need for more stringent control of cardiovascular risk factors in this disorder, endocrinologists are becoming increasingly involved in consultation and management. This involves both blood pressure control and management of hyperlipidemia. As mentioned earlier, hypertriglyceridemia is an independent risk factor for atherosclerosis, and this is particularly true for the diabetic; regimens need to be established to control this parameter as well.

**VI. Hormone Replacement Therapy**

As we have previously discussed, both estrogens and androgens have major effects on the cardiovascular system. As outlined by Drs. Liu, Death, and Handelsman in this issue of
Endocrine Review, there is controversy whether deficiencies of both of these classes of hormones, as occurs after menopause and andropause, result in an increased risk for developing cardiovascular complications. Most clinicians agree that replacement of androgens is indicated in men with testosterone deficiency. The argument for initiating estrogen replacement therapy remains controversial. As discussed earlier, recent studies using estrogen and progesterin replacement therapy failed to demonstrate improvement in cardiovascular risk in postmenopausal women, and trials with estrogen alone are ongoing. Because estrogens have complex actions on other tissues, including bone, uterus, breast, and the central nervous system, the decision to initiate estrogen replacement therapy has become more complex. Endocrinologists can be useful for advising patients and other clinicians in these situations.

Acknowledgments

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References

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16th INTERNATIONAL SYMPOSIUM of the JOURNAL OF STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY
“RECENT ADVANCES IN STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY”
5–8 June 2004—Seefeld, Tyrol, AUSTRIA

The following topics will be considered:

1. STEROID RECEPTORS, STRUCTURE, GENE EXPRESSION, AND MECHANISM OF ACTION. COACTIVATORS AND COREPRESSORS (INCLUDING STEROID MEMBRANE RECEPTORS)
2. NON-GENOMIC EFFECT OF STEROID HORMONES
3. STEROIDS AND CANCER (INCLUDING NEW PHARMACOLOGICAL APPROACHES IN ENDOCRINE-RELATED CANCERS)
4. STEROIDS AND THE BRAIN
5. STEROIDS AND THE MENOPAUSE
6. ANTI-STEROIDS
7. ENZYME MODULATORS
8. STEROID METABOLISM IN TARGET ORGANS
9. STEROID HORMONES AND THE ENVIRONMENT

Lectures (approximately 30-35) will be by invitation of the Scientific Organizing Committee and, in addition, there will be poster sections.

All abstracts for poster presentations will be subject to selection by the Scientific Organizing Committee. Abstracts (maximum 200 words) must be sent to: Prof. J. R. PASQUALINI by Monday, February 9th, 2004 (postmark) (Original + 4 copies).

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