In 1984, the adrenal pathologic findings in 4 Mayo Clinic cases of Cushing syndrome led to characterization of a unique disorder termed primary pigmented nodular adrenal disease (PPNAD). A literature review showed that the condition had occurred in 2 families. In 1 family, 2 siblings were affected and a third sibling without Cushing syndrome died of cardiac myxoma. To test the hypothesis that a connection existed between PPNAD and cardiac myxoma, J. Aidan Carney, MD, PhD, emeritus member of the Department of Pathology at Mayo Clinic in Rochester, Minnesota, searched Mayo Clinic files and the world literature for patients with both conditions.

Dr Carney recalls: “I noted in a Swiss report that 2 siblings with PPNAD had other disorders. One, aged 35 years, also had an eyelid ‘fibroma’ and became hemiparetic 4 years after adrenalectomy. The other, aged 37 years, was thought to have neurofibromatosis because of skin ‘fibromas.’ There was another odd finding in the family: a third sibling without Cushing syndrome or skin lesions died of left atrial myxoma at age 4 years. It seemed remarkable to haply find 2 disorders, a manifestly rare adrenal disorder (PPNAD) and another rare condition (cardiac myxoma) (and possibly a third [neurofibromatosis]), in a sibship and there not be a connection between them.”

Dr Carney continues: “But to entertain this hypothesis seriously, it was necessary to find at least 1 patient with PPNAD and cardiac myxoma. The 4 Mayo Clinic patients and the 19 patients with PPNAD identified in the literature were obvious candidates for the combination, but none had cardiac myxoma. Review of records of 131 Mayo Clinic patients who had undergone bilateral or subtotal adrenalectomy for Cushing syndrome up to 1982 showed that none had cardiac myxoma either. I tried another search approach: I reviewed the approximately 500 reported cases of cardiac myxoma and the 51 patients with cardiac myxoma operation at Mayo Clinic up to 1981, seeking cases that also featured Cushing syndrome. There were none. Up to that time, 29 additional Mayo Clinic patients had died of or with cardiac myxoma as an autopsy finding; none had Cushing syndrome. Review of pathologic diagnoses in these cases revealed 1 case with ‘multiple cortical (adrenal) adenomas.’ The gross description of the glands was ‘there are multiple cortical nodules in both adrenals. These are of a yellowish color, but contain some brown and black dots.’ The bilaterality and color of the nodules were reminiscent of PPNAD. However, there was no mention of cytoplasmic pigment or the bizarre.
cytologic features typical of PPNAD; apparently, the lesions were small, standard adenomas. In a desperate effort to complete what had been a time-consuming and psychically draining experience before finally abandoning the search, I reviewed the adrenal microscopic slides in the 29 autopsy cases. The slides arrived for study on April 24, 1982. What emotion I felt as I looked at those of the case of ‘multiple cortical adenomas.’ The patient had PPNAD! At that instant, the PPNAD—cardiac myxoma combination assumed a reality for me—it never crossed my mind for a moment that the concurrence of the 2 conditions might have been simply the chance occurrence of 2 rare disorders in the same patient.”

Dr Carney reports: “It was surely not accidental that the cardiac myxoma in the case had been attached in the left atrium at the junction of septum and posterior wall, not the fossa ovalis, the usual site for sporadic neoplasm. Cushing syndrome was not mentioned in the autopsy clinical abstract—which was surprising; PPNAD had been functional in all the cases I had identified up to then. The incongruity was partially explained when I found Crooke hyaline change in corticotroph cells, a telltale sign of hypercortisolemia. The clinical record was a revelation; I went through it with mounting excitement and almost disbelief. The medical resident who initially saw the patient noted an unusual skin finding: ‘deeply pigmented moles cover most of body.’ The finding was repeated elsewhere in the report: ‘pale, tranquil with numerous nevi also (on) mouth/ lips’; ‘she looks pale, somewhat puffy, numerous pigmented nevi’; ‘many pigmented moles’; and ‘myxomatous mammary fibroadenoma.’ As I read these observations, I had the eerie feeling that I was reading the description of an unrecognized syndrome. It seemed almost impossible (statistically) that all the patient’s conditions—PPNAD, unusually situated or multiple cardiac myxomas, numerous pigmented moles, and a myxomatous mammary fibroadenoma—could be encountered together in the particular circumstances in which they had been found and the events be unconnected. They must all be related; they must constitute a syndrome.”

Dr Carney’s discovery led to further studies that documented what is termed Carney complex. The syndrome is characterized by spotty skin pigmentation (pigmented lentigines and blue nevi on the face, including eyelids, vermillion lip borders, conjunctivae, and sclera); myxomas (cardiac, cutaneous, and mammary); testicular large-cell calcifying Sertoli cell tumors; growth hormone–secreting pituitary adenomas; and psammomatous melanotic schwannomas (Figure). The hypercortisolism in individuals with PPNAD is caused by multiple, pigmented, autonomously functioning adrenocortical nodules. Patients with PPNAD may present with the typical signs and symptoms of hypercortisolism, including central weight gain, hyperglycemia, proximal muscle weakness, purple-red abdominal striae, hypertension, and menstrual cycle disturbance. However, the patients tend to be young (<30 years), may have mild or severe signs and symptoms related to hypercortisolism, have marked osteoporosis (presumably due to chronic mild hypercortisolism), and may have cyclic disease. Baseline hormonal evaluation documents increased cortisol levels in blood and urine, suppressed corticotropin, suppressed serum dehydroepiandrosterone sulfate, and a paradoxical increase in urinary free cortisol with dexamethasone suppression testing.

Approximately half of patients with PPNAD prove to have Carney complex. Thus far, mutations in 2 genes have been associated with the disorder, PRKAR1A and PDE11A. However, because some families with Carney complex do not have mutations in 1 of these 2 genes, studies are ongoing to identify additional loci. In most familial cases, Carney complex appears to be autosomal dominant in inheritance. Germline mutations in PRKAR1A also may be present in patients with isolated PPNAD.

**Autonomic Testing in Patients With Diabetes Mellitus**

Autonomic testing has a key role in the evaluation of patients with diabetes mellitus who are troubled by orthostatic intolerance, syncope, flushing, bladder and bowel dysfunction, gastrointestinal tract distress, painful feet, anhidrosis, or hyperhidrosis. Signs and symptoms of cardiovascular autonomic neuropathy include loss of normal heart rate variability (resulting in persistent sinus tachycardia), exercise intolerance, orthostatic hypotension, and silent myocardial ischemia and infarction. Paola Sandroni, MD, PhD, of the Department of Neurology at Mayo Clinic in Rochester, Minnesota, says: “Heart rate variation that normally occurs with deep breathing (a test specific for vagal function) and the Valsalva maneuver (which elicits activation...
of parasympathetic [vagal] and sympathetic cardiovascular responses) may be absent in patients with even early diabetic autonomic neuropathy [Figure 1]. Advanced autonomic neuropathy in patients with diabetes may cause cardiac denervation and lead to fixed heart rate, painless myocardial infarction, and increased risk of death. Central and peripheral cardiovascular sympathetic denervation may result in postural hypotension due to the lack of vasoconstriction in peripheral and splanchnic vascular beds.”

Peripheral autonomic neuropathy results from loss of sympathetic vascular innervation, leading to vasoconstriction failure, abnormal local reflex vascular control, and increased peripheral blood flow through arteriovenous shunts. Furthermore, sympathetic fibers innervating sweat glands are lost. Signs and symptoms of peripheral autonomic neuropathy include venous prominence, peripheral edema, dry skin, pruritus, and poor wound healing—all of which may lead to foot ulcers.

In the 29 years since neurologist Phillip A. Low, MD, founded the autonomic testing laboratory at Mayo Clinic in Rochester, Minnesota, he and his colleagues have established the norms and national standards for quantified evaluation of autonomic function. In conjunction with the thermoregulatory sweat test (TST) and under the direction of fellow neurologist Robert D. Fealey, MD, since 1980, routine autonomic evaluation includes noninvasive tests of sudomotor, cardiovagal, and adrenergic function. Because test results are quantifiable, responses from the 3 systems can be compared to determine selective or relative autonomic dysfunction, or both. For example, a patient might have moderate cardiovagal system involvement and severe adrenergic function involvement without an impact on sudomotor function. Or cardiovagal and adrenergic systems may be normal in isolated anhidrosis, suggesting chronic idiopathic anhidrosis. This latter condition is a more benign disorder that does not progress to widespread autonomic failure and for which symptomatic and sometimes specific treatment is available. Only by testing all 3 systems can such diagnostically informative patterns emerge.

Dr Low explains: “Autonomic testing helps determine presence, severity, distribution, and localization of autonomic dysfunction. It can distinguish primary from secondary autonomic disorders, true autonomic neuropathy from conditions that mimic it, and psychogenic from organic conditions. It can help differentiate progressive diseases and serve to monitor disease progression and response to treatment.”

**Routine Tests of Autonomic Function**

**Sudomotor Tests**
The quantitative sudomotor axon reflex test (QSART) evaluates postganglionic sudomotor function. TST evaluates preganglionic and postganglionic function over the anterior body sur-
face (Figure 2). When assessed together in the same patient, TST and QSART can differentiate preganglionic from postganglionic lesions. For QSART, a stimulus solution of acetylcholine is applied with iontophoresis to evoke an axon reflex–mediated sweat response. Recording sites include forearm, proximal leg, distal leg, and proximal foot. TST uses a dedicated heat- and humidity-controlled cabinet to produce a whole-body sweat response that can be quantitated as a percentage of body surface sweating versus not sweating. Distribution of abnormal sweat responses is diagnostically important for various conditions (eg, peripheral neuropathy). For example, small-fiber neuropathy with the symptom of burning feet can be associated with idiopathic disease and also with diabetes. In such cases, the most distal sites may have abnormal QSART and TST responses, with more proximal sites becoming involved as the disease progresses. Using a 10-point composite autonomic severity score that they developed, Drs Sandroni, Low, and Fealey found that sudomotor testing is highly sensitive in identifying clinical distal small-fiber neuropathy in patients who have normal or unrelated abnormalities on electromyographic testing. Dr Sandroni notes: “This is a condition for which we get a lot of referrals. It is very difficult to diagnose unless carefully controlled sudomotor testing is done.”

Cardiovascular and Adrenergic Function Tests

The 2 main tests of cardiovagal function in the autonomic test sequence are heart rate response to deep breathing and the Valsalva ratio, which involves several calculations and up to 4 maneuvers. The Valsalva ratio measures beat-to-beat blood pressure. Once an invasive technique, its measurement can now be done with a recording device placed on the patient’s finger. Heart rate, systolic blood pressure, and diastolic blood pressure are displayed continuously on a computer screen (Figure 1). Valsalva maneuver is measured during 4 main physiologic phases. Drs Low and Sandroni and their colleagues have validated the use of the phases in evaluating adrenergic function. Beat-to-beat blood pressure under various laboratory conditions is a proven method of testing adrenergic function for many conditions, including orthostatic hypotension (OH) (Figure 3). OH is well recognized as a potential consequence of chronic diabetes and is recognized increasingly as a common disorder among elderly persons. Some OH symptoms (eg, fatigue, impaired concentration) can be subtle and OH difficult to diagnose. Even when mild, OH symptoms can be debilitating and markedly affect activities of daily living. Severe, sustained OH can induce syncope with resultant falls and injury. In younger patients, symptoms may include palpitations, anxiety, and nausea and may be indicative of autonomic neuropathy.

Adrenergic testing helps distinguish OH syncope from psychogenic disorders and from other conditions that induce loss of consciousness, such as seizures and transient ischemic attacks. Autonomic tests can determine OH severity, an important factor when considering behavioral, pharmacologic, and nonpharmacologic treatments. In discussing the value of Mayo’s autonomic testing laboratory, Dr Low notes that “it highlights the complexity of the autonomic system.” He continues: “Although we can’t dissect all aspects of autonomic function, what we can do is detect deficits that may have gone undiagnosed, determine whether problems are benign or represent true autonomic failure, and, if so, quantify its severity and distribution.”

Figure 2. Thermoregulatory sweat test in a patient with diabetes mellitus. Areas of normal sweating are shown in purple. This patient presented with somatic asymmetrical (left>right) radiculoplexus neuropathy, right thoracic radiculopathy, patchy small-fiber dysfunction, and autonomic neuropathy.

Figure 3. Tilt table study showing orthostatic hypotension without compensatory tachycardia. Green indicates heart rate; red, pink, and yellow, systolic, mean, and diastolic blood pressure, respectively.
Robotic Thyroidectomy

Thyroidectomy is a relatively new application of the surgical robot and allows completion of a total thyroidectomy and central compartment node dissection while avoiding neck incisions. Jan L. Kasperbauer, MD, of the Department of Otorhinolaryngology at Mayo Clinic in Rochester, Minnesota, says: “Robotic thyroidectomy is possible because of the excellent visualization provided by a high-resolution camera, wristed instrumentation promoting delicate and complex motions, and application of the harmonic scalpel to divide and seal vessels without ligature. Although most applications of the surgical robot can be considered minimally invasive, its application to thyroidectomy should not be considered minimally invasive because the incisions are more distant and, therefore, a greater dissection length is required for access.”

The surgical robot consists of a surgeon workstation (Figure 1) and a separate working platform with articulated arms in contact with the patient (Figure 2). Application of the gasless technique of robotic thyroidectomy was pioneered by Dr Woong Yoon Chung of Yonsei University College of Medicine, Seoul, South Korea. The need to avoid scars in a population with a high incidence of keloid formation and negative social stigma associated with neck scars provided the impetus for this approach. Dr Chung’s work forms a benchmark for early adapters in the United States and elsewhere.

Dr Kasperbauer explains: “Access for the camera and instruments to reach the thyroid and central neck is acquired by an incision of approximately 6 cm in the anterior axillary fold and a separate small skin incision adjacent to the sternum [Figure 3, on page 6]. Elevation of skin and subcutaneous tissues off the pectoralis fascia and lower neck muscles provides working space. The camera and 2 working arms are placed through the anterior axillary fold incision and a separate working arm is placed through the separate skin incision adjacent to the sternum. The 30° camera angle and harmonic scalpel allow the surgeon to perform a near-total thyroidectomy and central compartment node dissection if indicated.”

Ideal surgical candidates have indeterminate thyroid lesions less than 4 cm in diameter or confirmed papillary thyroid cancers less than 2 cm in diameter that do not extend to the posterior portion of the gland. Dr Kasperbauer notes: “Patient body habitus must be taken into consideration, and obese patients are not candidates. As with most procedures, gradual expansion of indications will occur as experience builds. Current contraindications to the robotic approach include lateral neck nodes, papillary cancers larger than 2 cm in diameter or located in the posterior portion of the gland, and indeterminate lesions greater than 4 cm in diameter.”

To determine the safety, applicability, and
outcomes associated with robotic thyroid surgery, Dr Kasperbauer and colleagues have established a prospective study at Mayo Clinic in Minnesota. This investigation was initiated after performing procedures on cadavers and observing robotic thyroid surgery performed by Dr Chung in South Korea. Dr Kasperbauer comments: “Early experience with lobectomy and near-total thyroidectomy with central compartment dissection in our patients has been rewarding without permanent hypocalcemia or vocal cord paralysis.”

John C. Morris III, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “It is important for patients and endocrinologists to understand that robotic thyroidectomy is not minimally invasive and is not the standard of care. The main advantage of robotic thyroidectomy is cosmetic—no neck surgical scar. The standard with which we need to compare outcomes is the open-collar incision for access to the thyroid gland, which in experienced hands is very safe, effective, and well accepted. Until we learn more, robotic thyroidectomy should be reserved for patients who, for cosmetic reasons, wish to avoid a neck scar in exchange for an incision and scar in the anterior axillary fold.”

### Diabetes and Cancer

The US incidence of both diabetes mellitus and cancer is increasing. Approximately 1.6 million new cases of diabetes mellitus and 1.4 million of cancer are diagnosed every year. Pankaj Shah, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “Evidence suggests that these 2 common conditions coexist more often than would be expected to occur by chance. Large cohort studies show that pancreatic, colorectal, breast, hepatobiliary, bladder, and endometrial cancers occur more frequently in people with type 2 diabetes. Potential reasons behind this association include common causality (shared risk factors), hyperglycemia and other metabolic abnormalities of type 2 diabetes that cause cancer, and cancer that causes hyperglycemia.”

Older age, male sex, obesity, diminished physical activity, a diet high in calories and glycemic index, excessive alcohol intake, and tobacco smoking are associated with increased risk of diabetes, as well as many cancers. Dr Shah explains: “A common thread for many of these risk factors is hyperinsulinemia [Figure]. Insulin induces cell proliferation. Hyperinsulinemia, insulin resistance, and obesity are associated with increased estrogens, endometrial hyperplasia, and breast and endometrial cancers. Obesity is also associated with increased insulinlike growth factor 1 (IGF-1) activity due to reduced levels of insulinlike growth factor binding proteins 1 and 2. Most malignant cells express IGF-1 receptors. Activation of IGF-1 receptors by IGF-1 or insulin, or both, is thought to have an important role in carcinogenesis. Whether exogenously administered insulin used to control hyperglycemia promotes cancer growth in vivo is still an open question.”

In 1956, Otto Warburg proposed that cancer cells preferentially use large amounts of glucose through glycolysis to produce lactate, whereas most nonmalignant cells completely

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**Figure.** Potential mechanisms linking cancer and type 2 diabetes mellitus. IGF-1 indicates insulinlike growth factor 1; SHBG, sex hormone–binding globulin.
oxidize glucose through the citric acid cycle. Potential mechanisms linking cancer and type 2 diabetes include the following:
- Glycolysis upregulation may support carcinogenesis. Cancer cells may have a defective mitochondrial metabolism and may have overexpression of the glucose transporter GLUT-1.
- Hyperglycemia may be responsible for excess glucose supply to these glucose-hungry cells, resistance to apoptosis, oncogenesis, and tumor cell resistance to therapy. However, hyperglycemia associated with type 1 diabetes is not associated with these cancers. Moreover, hyperglycemia correction has yet to show reduction in cancer incidence in people with type 2 diabetes.
- Hyperglycemia and hyperinsulinemia are associated with endothelial proliferation and neovascularization (in the retina). Vascular growth is essential to the fuel supply required for malignancy maintenance. Therefore, it is conceivable that vascular growth is stimulated in people with type 2 diabetes, thus promoting cancers.
- Some cancers (eg, pancreatic cancer) are associated with newly diagnosed diabetes.
- Cytokines and other substances released from cancers can cause hyperglycemia by inducing insulin resistance.
- Cancer-related decreased physical activity can reduce insulin sensitivity.
- Cancers are associated with varying degrees of cachexia, and cachexia-associated muscle wasting leads to insulin resistance.

Managing Diabetes in Patients With Cancer
Treating diabetes in a person with active cancer is often complicated by the cancer, cancer therapies, and the adverse effects of treatment (eg, anorexia, nausea, weight loss). Acute diabetes complications and the urgency of treating severe hyperglycemia may delay cancer treatment. Dr Shah advises: “Tight glycemic control carries clinically important risks without clear benefits in patients with cancer. The goals of therapy should be to prevent marked hyperglycemia (>180 mg/dL) and the adverse effects of treatment (eg, hyperglycemia, anemia, increased risk of fractures). Hyperglycemia first recognized during cancer therapy should not be neglected, and the patient and the family should be taught to monitor blood glucose concentrations. Hyperglycemia can and possibly will occur again during subsequent treatment cycles. If hyperglycemia is recognized and appropriately treated, severe acute hyperglycemic complications can be prevented. The health care provider must understand the patient’s distressing situation. We take special care to share with the patient and the family that we understand their difficult situation. We tell them that we know that they are likely overwhelmed by the complexity of their multiple therapies and the adverse effects emanating from cancer and cancer therapies. Usually, this conversation is followed with clarification of the purpose of home glucose monitoring and hyperglycemia therapy. We stress that our goal is to prevent severe acute hyperglycemic and infective complications while avoiding complications from hyperglycemia therapies and ensuring timely optimal cancer therapy. Patients often participate in the decision making about the goals and modes of hyperglycemia therapies.”

Choosing Antidiabetic Agents
Marked hyperglycemia is associated with poor outcomes in cancer patients. Thus, most experts recommend treatment of severe hyperglycemia. Growing evidence shows that metformin use is associated with lower cancer incidence and lower cancer mortality rate than treatment with sulfonylureas or insulin. The adenosine monophosphate-activated protein kinase (AMPK) pathway is involved in cancer growth, and metformin activates AMPK. Currently, 10 studies registered at clinicaltrials.gov are investigating possible benefits of metformin in cancer patients. These studies include patients with advanced cancers and patients with breast, pancreatic, and prostate cancers. Mutation of peroxisome proliferator-activated receptor γ (PPAR-γ) is involved in carcinogenesis. Thiazolidinediones are PPAR-γ agonists and are being investigated to see whether they enhance outcomes from anticancer therapy in patients with breast, lung, prostate, and head and neck carcinomas; sarcoma; and premalignant conditions.

Clinical Use of Antidiabetic Agents
Dr Shah recommends: “If tolerated and not contraindicated, metformin is the first-line oral agent. Metformin may cause nausea and diarrhea, which can be confused with complications of cancer or its therapies. Insulin is usually effective in controlling severe hyperglycemia. In our experience, ‘intensive insulin therapy’ using multiple insulin injections may be easier, providing the patient with freedom of time and amount of food. The so-called sliding scale insulin regimen is associated with the worst glycemic extremes and should be avoided. If diabetes is treated with agents that predispose to hypoglycemia (eg, sulfonylureas, other insulin secretagogues, intermediate-acting or mixed insulin), meals should be timed throughout the day. When life expectancy with terminal cancer is brief, blood glucose monitoring is performed only when symptom control requires it, with the sole aim of making the person comfortable.”
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