Many of the ideas contained in ***The Potbelly Syndrome*** were first published in the form of a medical puzzle for doctors in the Winter 2001 issue of *Clinical Practice in Alternative Medicine* (CPAM). The article is reproduced below with the permission of the Editor of CPAM.

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Short Communication

The Mysterious Afflictions of Miss M.G.

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First I want to present a diagnostic puzzle, then some comments, and finally a question.

Imagine that every year you spend two weeks working in a third-world clinic with limited and archaic laboratory facilities. You can, however, send specimens to a modern laboratory and get the results back by email in a few days. One of the patients you will see today is a Miss M.G., whose medical file includes the following notes, written by a Dr. X two years previously:

- Miss M.G. is from a large and healthy family. At age 21, her height is 4' 9". She has a delicate frame with small extremities. She weighs 112 pounds.
- She feels chilly and cold all of the time and suffers from insomnia. Muscular weakness is extreme, and she complains of backache and epigastric pains.
- Other symptoms include diplopia, eye pain, insomnia, tinnitis, frequent sore throat, and shortness of breath.
- Cardiovascular exam is negative except for palpitation and BP of 185 mm Hg.
- Her blood shows no abnormalities; RBC 5,300,000/cmm, WBC 12,000/cmm, Hgb 85%. Coagulation time 3 is minutes. Serologic test for syphilis is negative.

What do you think was causing Miss M.G.'s problems?

On the next page you find the comments of a Dr. Y, made one year ago. She begins by saying that most of Miss M.G.'s earlier symptoms are still present, and then adds the following:

- At age 22, Miss M.G. exhibits marked adiposity, limited to her abdomen and neck. The fat is coarsely nodular and painful. Skin is rough and extremely dry. Her menses stopped several years ago.

- She exhibits bilateral exopthalmos.
- Her skin bruises easily and large spontaneous ecchymoses occur frequently.

What other tests should Doctor Y have asked for?

When you examine Miss M.G., you find that most of the symptoms described by Drs. X and Y are still present in the unhappy young lady. Furthermore, she has gained 25 pounds in the last two years and looks like she is at the end of a full term pregnancy. She has purple striae over her abdomen. Her round, moon-shaped face is covered with a fine growth of hair, particularly her forehead and upper lip. She is losing the hair on the top of her head, however.

By now you have guessed that Miss M.G. is suffering from severe hypercortisolism. She is, in fact, Harvey Cushing's Case XLV, which he described in 1912,[1] about thirty years before the term "Cushing's syndrome" (CS) came into use.

I did not list all of Miss M.G.'s symptoms because the purpose of this exercise was not to test your skill at diagnosing frank CS, which you can probably do from fifty feet if the light is good, but to draw your attention to the symptoms of subclinical CS, the symptoms found by Drs. X and Y.

The subtler forms of hypercortisolism, which are often misdiagnosed as diabetes, are thousands of times as common as full-blown Cushing's syndrome. Autopsy studies, for example, indicate that 25% of the people in the U.S. have pituitary tumors.[2] A brief review of related studies suggests that about 5% of these tumors produce ACTH.[3-7] If these figures are accurate, then there may be 3.5 million cases of pituitary-induced hypercortisolism waiting to be diagnosed.

In the Eighties there were a few papers describing accidentally-discovered adrenal tumors dubbed "incidentalomas." Since the advent of ultrasound, computed tomography, and magnetic resonance imaging, thousands more of these tumors have been found, and many of them secrete cortisol. Reincke *et al.* examined eight women with cortisol-producing incidentalomas.[8] Only one of these women had a cortisol level above the NIH reference interval (5-25 µg/dL), but they were not, as a group, healthy people. Seven of them had hypertension, four were obese, and two had type 2 diabetes.

After their cortisol levels were lowered by surgery, the women's blood pressures and weight dropped and those with diabetes had better control of their blood sugar.

In a larger study, Rossi *et al.* examined a series of 50 patients with incidentalomas. These patients had many symptoms of hypercortisolism even though very few of them had cortisol levels above 25 µg/dL. The subset of 12

patients that met their definition of subclinical CS were in even worse health (Table 1).[9]

Table 1. Symptoms of patients with adrenal incidentalomas.

Symptoms	All 50 patients	12 patients with subclinical CS
Mild to severe hypertension	48%	92%
Obesity	36%	50%
Abnormal lipids	28%	50%
Type 2 diabetes	24%	42%
Glucose intolerance	12%	--
Mean morning cortisol levels	18.9 μg/dL	18.1 μg/dL

All of the patients who were treated for their hypercortisolism improved. There is virtually no chance that their hypercortisolism would have been detected without the happy accidents that revealed their incidentalomas.[10]

How many people have growths on their adrenal glands? No one knows, but Marchesa *et al.* found that 7.4% of the patients undergoing abdominal CT scans at their facility had adrenal incidentalomas.

Another newly-discovered source of cortisol is fat. Many tissues protect themselves from excess cortisol by converting it to cortisone, but adipose tissue reconverts cortisone back to cortisol.[11] More research is needed to determine the health effects of fat-derived cortisol.

Iatrogenic hypercortisolism is more common than most people suppose. Dr. David Orth, a researcher from Vanderbilt University and a member of the medical advisory board for the Cushing's Support & Research Foundation, estimates that 250,000 people develop CS every year as a result of taking cortisol-like medicines.[12] The U.S. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) describes the side effects of these medicines as follows:

> . . . changes in appearance (such as acne or increased facial hair); development of a round or moon-shaped face; thin, fragile skin that bruises easily; or movement of body fat to the trunk. You might also experience mood changes, personality changes, irritability, agitation, or depression. Other possible side effects include increased appetite and weight gain, poor wound healing, headache, glaucoma, irregular menstrual periods, peptic ulcer, muscle weakness, osteoporosis, steroid-induced diabetes, and osteonecrosis (damage to the hip joint that leads to severe arthritis).[13]

NIAMS should have added insulin resistance to its list. One of cortisol's most important functions is to raise blood sugar levels by inducing temporary

states of insulin resistance. Chronic hypercortisolism results in chronic insulin resistance. Insulin resistance, of course, is the central element of Reaven's Syndrome X. For more information on the links between cortisol and Syndrome X, see the numerous papers of Brian Walker and Per Bjorntorp.[13-19]

There is one more source of excess cortisol that dwarfs all of those described above, and that is infection. HIV patients, for example, have elevated cortisol levels at all stages of infection and many of them have Cushingoid fat deposits on their necks, upper backs, chests, bellies and behind their ears.[20-23] The sizes of their fat deposits are closely correlated with their cortisol production.[24]

In 1986, Robert Da Prato and Jonathon Rothschild suggested that the AIDS virus raised cortisol levels enough to inhibit the body's anti-AIDS strategies and produce what they called a "self-sustaining downhill clinical course."[25] Many common infections raise cortisol levels even higher than HIV does, raising the possibility that there are millions of Americans whose chronic infections are complicated by similar cortisol-infection-cortisol loops.

Chlamydia pneumoniae (CPN) may initiate such a cortisol loop. There is abundant evidence that CPN thrives when cortisol levels are high.[26-30] The evidence that CPN raises cortisol levels is fuzzier, but there are two reasons to suspect that it does:

- CPN—even parts of dead CPN—stimulate the production of IL-1, IL-6, and TNF-alpha, all of which raise cortisol levels.[31-32]
- Several of the diseases linked to CPN—obesity, diabetes, stroke, cardiovascular disease—are also linked to high cortisol levels.

Finally, here is my question. Given the likely high prevalence of hypercortisolism, and the fact that cortisol blood levels are often normal despite hypercortisolism, how can alternative medicine help physicians to diagnose and treat the subtler forms of hypercortisolism that I have described? I hope that readers of this *journal* will respond with letters to the editor.

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