The topic of *paraneoplastic syndromes* has been on my “to do” list, but it has taken far too long… so let’s get to it.

*Paraneoplastic* means alongside cancer, and that’s because they are weird manifestations not of the cancer that are caused directly by the tumor but at distant sites from the cancer, such as by the cancer turning up the production of a protein or peptide (piece of a protein). They really aren’t being mass-produced as part of the cancer’s needs, but more of a side effect, just copying these genes that happen to be innocent bystanders. Another potential mechanism of these syndromes is stimulation of an antibody response by the body, and these antibodies against the cancer cross-react against normal body cells, turning the immune system against the body (causing an *auto-immune* disease). This is commonly against neurons in the setting of SCLC. The cells of origin for SCLC are neuroendocrine cells, so deranged cells starting as neuroendocrine can have features that look similar to the immune system to neurons, and the endocrine portion means that these cells have differentiated to have a good ability to package proteins and peptides. With that background, it shouldn’t be a surprise that SCLC is the most common form of cancer to be associated with paraneoplastic syndromes. And these can be associated with a HUGE range of symptoms from low serum sodium levels (caused from a *syndrome of inappropriate anti-diuretic hormone*, or SIADH) to neurological disorders like Lambert-Eaton myasthenic syndrome, and everything in between.

Most cancers that produce various proteins actually produce a sloppy version that has lower biological effect than the proper version of the protein. However, they often produce such a vast quantity that even weakened versions can still have important biological effects. Sometimes they produce huge quantities of a precursor protein that is subsequently converted to the active form by the body. Finally, sometimes they convert a less active precursor to a more active version of the protein, thereby conferring excess biological activity by upsetting the balance between apprentice and master proteins.

Just to give a sense of some of the proteins can be produced, here’s an incomplete list:
Introduction to Paraneoplastic Syndromes

Pro-opiomelanocortin and related peptides
Corticotropin-releasing hormone
Chorionic gonadotropin and its subunits (α and β)
Vasopressin
Cytokine growth factors (e.g., TGF-β, EGF, IGF-II)
Parathyroid hormone–related protein
Parathormone
Erythropoietin
Eosinophilpoietin
Growth hormone
Growth hormone–releasing hormone
Prolactin
Gastrin
Gastrin-releasing peptide (and bombesin)
Secretin
Glucagon
Calcitonin
Renin, prorenin
Vasoactive intestinal peptide
Somatostatin
Hypophosphatemia-producing factor
Endothelin-1

What do all of these do? Don’t ask — that’s an entire physiology course. But this gives a flavor of the myriad things that can go wrong just as paraneoplastic syndromes in cancer.

Cancers can also produce “cytokines” that can have effects like juicing the bone marrow to make more blood cells, similar to leukine or neupogen made by the tumor and producing very high white blood cell counts, in the range that doctors may think someone has a serious infection or even leukemia. Cytokines may also lead to high blood calcium levels caused by the tumor triggering cells to break down bone tissue and dumping the calcium into the bloodstream.

Although only a small proportion of people with a given cancer have these syndromes, but when they are seen, certain syndromes make us think of cancer. For instance, Lambert-Eaton myasthenic syndrome is a neurological disease caused by development of antibodies to a part of the spinal cord neurons that triggers muscle activity, and approximately 60% of patients with Lambert-Eaton syndrome also have SCLC. Similarly, about half of the people who develop a form of neurological degeneration of the cerebellum, a part of the brain that coordinates coordination and balance, have identifiable antibodies that trace back to a particular type of cancer.
One potentially useful effect related to this process is that cancers often turn on production of fetal proteins. These are not typically associated with symptoms, but proteins like carcinoembryonic antigen (CEA) (elevated in a wide range of cancers, including lung cancer) and alpha-fetoprotein (AFP) (elevated in hepatocellular (primary liver) cancer and some testicular cancers) as well as others can potentially be useful as serum tumor markers that may offer a blood test-based window into the status of a cancer.

So what can you do about paraneoplastic syndromes? Some that are mediated by autoimmune responses, such as Lambert-Eaton syndrome, can potentially be treated with immunosuppressive medicines, but the cornerstone is to treat the underlying cancer, the root of the problem, as effectively as possible. Easier said than done. In the meantime, as if cancers weren’t tough enough to manage already, paraneoplastic syndromes often add a curveball.