

## No stone unturned?

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**I** PEER REVIEW ARTICLES submitted to a large number of medical journals. Since I publish a fair amount in peer-reviewed journals, I have a duty to provide evaluations for others. I am apparently an easy mark, since I get asked a lot. Recently I've been impressed with the time, effort and money investigators are spending performing high-quality research on low-quality questions. As a reviewer I get to help decide whether the article sees the light of day or not. At a competitive journal, one bad review probably kills the paper, unless the reviewer betrays a lack of understanding or a bias. My reviews on these articles informs the editors that I think the study was well done, the manuscript well written but that the time spent on the project and the time spent reading the result would have been more profitably spent elsewhere.

Most of these articles aim for low-hanging fruit. The term, "low-hanging fruit" usually refers to easy to obtain results for new problems. If no one recognized that people with a certain disorder have an unusual problem, then the first few papers describing this reap the reward of the early recognition of the problem, thus harvesting the low-hanging fruit.

For example, when gambling was first reported to be a substantial problem in Parkinson's disease patients treated



with dopamine agonists, the first several papers were simply epidemiological studies, determining if this was, in fact, a problem, and then what the prevalence and risk factors were. These were important questions requiring answers, and the methodology was clear. All one needed was

a few hundred patients with PD, which was readily available at any movement disorders clinic in the world, and the time to question the patients. The harder questions came later, trying to figure out what the pathophysiology was. That work continues.

I've recently discovered that there is another meaning to low-hanging fruit. First I read a paper reporting an inverse correlation between strength in a leg muscle and cognitive function in old people. While this may seem like hot stuff, there had already been inverse correlations between physical activity of various types and dementia, between strength in arm muscles and dementia and a variety of other physical factors, all of which indicated that the more active, the better in shape someone was, the less likely they were to be demented. One may want to posit a chicken-and-egg question, but the paper I read didn't bother to do that. It simply extended the known relationship between an arm muscle and dementia to a leg muscle

and dementia. The study had been funded by a federal agency in another country, and the study had been well performed. The question I had was: Why would anyone care?

Then I was asked to review a paper which found a correlation between a blood lipid and one neuropsychological function in people with Parkinson's disease. The main reason I agreed to review the paper, other than the fact that I have difficulty saying no to reasonable requests, since, after all, someone has to do it, was that I wanted to see how the argument was made for undertaking the study.

Another recent paper was a study of movements during sleep of people with PD. This required overnight polysomnograms and videos to track movements and sleeping positions. It concluded that PD patients lie on their back more than age-matched controls, and moved less. Duh! The rationale for undertaking such a mattress-breaking study was that data from other studies had shown increased negative health measures in people who slept long periods of time on their back and didn't move much. The idea that a health problem, maybe something like PD, causes the health problem, or was the health problem, and that this disorder produced less movements during sleep was not discussed. The authors concluded that future health-related, quality-of-life measuring instruments should inquire about sleeping on one's back.

There are always justifications to be made for any study. After all, the more you learn, the more you know and who knows what interesting and useful discovery will be made when the next rock is turned over? When I mull these questions over I wonder about all the other self-evident truths that turned out to not be true when tested, or silly-sounding hypotheses that, when investigated, become pillars of contemporary medicine. For how many years was the *Helicobacter pylori* infectious theory of ulcers disparaged? I could not imagine why our major neurology journals published articles on olfactory disturbances in Parkinson's disease 15 years ago. I figured, "Who cares?" Of course, it turned out that this is a common "pre-motor" feature of the disease, and, while certainly not a cause for concern in older people developing olfactory impairment, it nevertheless

is impaired in 70% of PD patients by the time they develop their first motor manifestation, and, when added to other non-defining, but common pre-motor features of the disease, like constipation, cardiac sympathetic denervation, depression and fatigue, can help identify a population at markedly increased risk of developing the illness. This will be important in developing trials and later treatments, for people at the earliest stages of the disease. In addition, the olfactory observation led immediately to the hypothesis that perhaps a substance, whether infectious or toxic, enters the brain via the nerves to the nose, as the olfactory tubercle is, in fact, an early site of disease pathology. Speaking as a skeptic, though, I generally take the tack that if you ask a stupid question you're bound to get a stupid answer. A reviewer needs to

be very smart or insightful to be able to distinguish stupid from innovative. Few of us are. I only hope that I have not squelched that seemingly idiotic waste-of-time study that turns out to be iconoclastic in one of my reviews. I think about the reviewers at the publishing houses which turned down the first Harry Potter book. ❖

#### Author

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## Downton Abbey's 'Medical' Finale

HERBERT RAKATANSKY, MD

**T**HE FINAL SEASON OF Downton Abbey resolves most of the characters' personal problems but several medical issues remain challenging.

Lord Grantham, who had previous abdominal pain, had an episode of hematemesis during a formal dinner. He was taken to the local hospital, which was in the process of merging with a larger metropolitan institution. The merger was controversial with the local community afraid of distant control and an impersonal, lesser quality of care. Then, as now, the merger went through. And there he had an operation for his "ulcer."

In 1925 he would have had a partial gastrectomy with a (newly described) posterior gastrojejunostomy. A vagotomy would not have been done as that procedure was introduced by Lester Dragsted at the University of Chicago in 1943.

Subsequent complications including nutritional issues, weight loss, dumping syndrome and anastomotic ulcers were common. Lord Grantham, however, recovered uneventfully and developed none of these.

Additionally one wonders if he had transfusions. Although there were early sporadic reports of transfusion, it was not a useful tool until Landsteiner discovered the blood groups in 1901,



winning him the Nobel Prize in 1930. Reuben Ottenberg administered the first transfusion using blood typing at Mt. Sinai Hospital in NY in 1907. The first "transfusion center" was established by Percy Oliver (associated with the British Red Cross) in London in 1921. That London center

maintained a roster of persons, pre-screened for syphilis, with known blood types. If a transfusion were needed, a donor would personally go to the hospital for direct transfusion. There were 428 such donations in 1925. London was a train ride away from Downton, so it is unlikely, but possible, that Lord Grantham received a transfusion.

The use of citrate to anticoagulate blood was reported in 1915 but was not adopted rapidly. In 1936 SS Yudin (Leningrad) reported almost 1,000 cases of transfusion of defibrinated cadaver blood stored for as long as 3 weeks, a technique not adopted by others. The first modern blood bank using bottled blood from living donors was established by Bernard Fantus at Cook County Hospital in Chicago in 1937. Blood was stored for up to 10 days.

### Lord Merton's anemia

In the final episode Lord Merton felt weak, had some tingling and initially was diagnosed with pernicious anemia,

at that time a fatal disease. He was later told that "tests" revealed iron deficiency anemia and that he would do well. Anemia was well known but poorly quantified in 1925. Manual RBC counts were routine. But colorimetric quantitative analyses of hemoglobin were inaccurate with no accepted normal standards. The hematocrit, introduced by Wintrobe in 1929, finally enabled an accurate measurement of anemia. Also, in 1929, Wintrobe conceived of calculating the RBC indexes, an idea that "came to me in the middle of the night."

The discovery of Carl Weigert and Paul Ehrlich in 1877 that tissues and blood cells could be stained enabled microscopic examinations of the marrow and peripheral smear. Macrocytosis could be identified, but only by examination of smears. Reticulocytes were recognized as early RBC's. Megaloblasts in the marrow were first described in 1921 and hypersegmented WBC in 1923. Perhaps these were the "tests" that excluded the diagnosis of pernicious anemia in Lord Merton.

In 1926 George Minot and William Murphy reported the successful treatment of 45 pernicious anemia patients with a diet including ¼ to ½ pound of liver and ¼ pound of red meat daily for two years. The response to liver therapy was monitored by reticulocyte and RBC counts. Injectable liver extracts followed quickly but B12 was not isolated till 1948. In retrospect that quantity of liver contained enough B12 to allow passive

diffusion. Minot and Murphy shared the Nobel Prize in 1934.

In 1925 anemia characterized by small RBC was known as “simple anemia.” The RBC count in iron deficiency may not be very low, though the cells are small and lack adequate hemoglobin. The concept of iron deficiency due to “nutritional” issues was recognized, but anemia as a distinct entity due to iron deficiency was not suggested until DT Davies and LJ Witts separately suggested the association of hypochromic anemia and a lack of iron in 1931. Thus it was not possible in 1925 that Lord Merton could be diagnosed specifically with iron deficiency anemia.

But we know now that if a man of Merton’s age developed iron deficiency anemia it likely would have been no less dangerous (in 1925) than pernicious anemia. GI cancer, celiac disease, H pylori, etc. were either unknown or untreatable. In this scenario there would be no happy ending for Lord Merton. A

diagnosis of pernicious anemia might have been more hopeful. If he had survived into 1926 and had the opportunity to receive liver therapy he might have done well. But Merton might have had anemia of chronic disease, though there was no allusion to an underlying illness. With no more episodes of Downton Abbey forthcoming, we will never know his fate.

### Mr. Carson’s tremor

And then there is the estimable Mr. Carson, the paradigm of properness. It was sad indeed to see him embarrassed by a tremor so severe that he could not pour the wine at dinner. It appeared to be an intention tremor that, in the “happy ending,” would be diagnosed as an “essential tremor.” While bothersome, it would not be fatal.

Mr. Carson subsequently admits, however, that he had been afraid of developing this problem since his father and grandfather had similar symptoms.

Carson’s observation that “I am done for!” also suggests that his father and grandfather had more than a mild disability. Parkinson’s rarely may be due to a monogenic autosomal dominant mutation. These mutations may be accompanied by dementia and other CNS degenerative processes, producing a progressive downhill course. More details about the clinical course of Carson’s father and grandfather would have helped predict his prognosis. As with Lord Merton, Carson’s fate remained uncertain.

An understanding of the medical issues of those times, even if occasionally erroneously described, enhances the narrative that has captivated so many viewers. ❖

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