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Small Research

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THERE ARE MANY STUDIES that need to be done to improve medical treatment. We worship the cult of evidenced-based medicine, ignoring the fact that the evidence often doesn't reflect the patients we're applying it to because they would have been excluded from study participation. We



use drugs for off-label indications because no one will pay for a study that proves a treatment might work on-label.

I don't think I'm a troglodyte in these matters. But I'm increasingly annoyed by the daily clinical questions we face that are relatively easy to solve, but cannot be because they are un-fundable. I've planned four studies that will answer potentially important clinical questions, at least in the world of Parkinson's disease, that simply require the administration of questionnaires to consecutive subjects, who are simply consecutive patients who agree to participate. None of these studies are of earth-shattering importance, but are sufficiently relevant to justify publication in a major neurological journal if the studies are done correctly and have interesting results. And, more importantly, might improve care. However, there is no possibility that any of these studies could possibly be funded. I can do these only because a student asked to do a research study. I don't think this

scenario is much different than it has been over the past several decades.

There are few funding mechanisms. The NIH funds major studies, requiring hundreds of thousands of dollars, most of which are big-ticket items costing millions, to answer very important questions involving thou-

sands of patients. These are crucial studies and the results do, in fact, alter our treatments, and, even if the benefits are meager, they apply to tens of thousands of people. On the other hand, studies of symptoms like fatigue, apathy, feelings of tremor internally may cost more to design for an NIH grant submission than to carry out. A study that might require \$20,000 of a study coordinator's time would probably require significantly more than that to simply put together a submission to the NIH, and stands less than a 15% chance of ever being funded and, even if funded, usually requires at least two submissions and a year's worth of effort.

I spent a decade trying to prove that clozapine was the treatment of choice for psychosis in Parkinson's disease. I was assured by many senior colleagues that a grant submission to the NIH would be a waste of time since that wasn't the sort of study they liked to fund at the time. The neurological institute wasn't interested in psychiatric

problems, and the psychiatric institute wasn't then interested in problems from neurology. The drug company that had the drug under patent wasn't interested in funding the study because of fear that the frail population was at too high a risk for side effects (read law suits) and the market was too small to justify it. So it was only after a colleague suggested applying for an FDA orphan drug grant that the study was funded. The maximum grant allowed still underfunded the study, but was sufficient for it to be done, with a lot of unpaid participation by my highly motivated colleagues. Not only was the drug company not interested in funding the study, they actually tried to renege on supplying free drugs, which it had promised.

Small research, in my view, is like "small ball" in baseball. It involves chipping away at the edges – bunts, stolen bases, hit and run, rather than home runs. To do small studies requires volunteerism. The patient advocacy organizations are primarily interested in cures. The NIH is interested in "big picture" projects which must be performed with incredible amounts of detail and statistical analysis. They also require pilot information, for which mechanisms for federal funding via competitive grants were recently developed. Drug companies are interested primarily in studies that can be used for marketing. Even getting IRB approval for studies where a few questions are asked requires an investment of several

hours. So, for example, if I want to find out how many of my PD patients suffer from anxiety, and how severe it is, I will need IRB approval, and then written informed consent to have patients rate their anxiety on a scale of 0–10. If I ask the question as part of a routine office visit, and record the answer, I can then obtain IRB approval for a chart review, thus obviating the need for informed consent, speeding up the process.

I am frustrated, and I'm unsure if I really should be. There is a limited amount of money available and endless numbers of important research questions. Our colleagues' abuse of patients, from the syphilis projects at Tuskegee, to the U.S. military's use of unknowing soldiers for experiments involving

radiation or mind-altering drugs, to Willowbrook, led to our use of IRBs to protect patients from abuse, and now to our increasing use of them to protect the institution from law suits.

I think I'm grumpy because I have less time to do the studies I used to do on my own time. The press of the financial vise in medicine has made "small research" increasingly difficult. Even involving residents in collaborative research projects is challenging since they have too little time to do their clinical work due to time restrictions without concomitantly reduced workloads. Luckily there are students who can afford to offer unpaid summer time either out of interest or to buff their resumes before applying to medical school. ❖

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The Origins of the Sneeze: Divine Gift or Mere Goldenrod Pollen?

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THERE ARE SOME WHO become so dismayed by monosyllabic words of robust Germanic origin that they compulsively seek out polysyllabic terms inherited from the two ancient Mediterranean cultures. And so, when they are obliged to acknowledge a sneeze, they will pause, seek through their thesauruses and then brightly declare: “’Tis not a sneeze, it’s a *snatiation*.’ ”

Snatiation, with its four syllables, sounds more cultured and eminently more authoritative. (Truly, a word not to be sneezed at.) Sadly, though, it is



neither Greek nor Latin in origin. Instead, it is an acronym for Sneezing Non-controllably At a Time of Indulgence of the Appetite – a Trait Inherited and Ordained to be Named, and was specifically contrived in 1990 by the geneticist, J.G.Hall, to bring comfort to those feeling diminished by the use of monosyllabic words.

Sneezing has not gone unnoticed in the ancient texts. Xenophon the historian relates that sneezes were regarded by the armies of Athens as good omens. And Greek mythology is awash with sneezes and their consequences.

Yet other humans are burdened by paroxysms of sneezing after an unduly heavy meal (for want of a better name, this is called The Achoo Syndrome).

Odysseus, after years of indolent island-hopping, and now disguised as a beggar, ventures home to his wife, Penelope. Her son, Telemachus, then sneezes, bringing her much joy since it is a divine sign that Odysseus has returned.

The Romans, however, had a more conventional word for sneezing, the English spelling of which is *sternutation*. Sneezing in the Roman Empire, and its formulaic responses, had become so common that Pliny (23–79 CE) had idly wondered, “*Cur sternutamentis salutamus!*” (Why greet sneezings?)

Indeed, why greet sneezes? And why not sniffles, snorts, sneers or even coughs? Yet every known culture has determined that sneezing is an involuntary act and clearly a divine omen. Some cultures have then decided that sneezes are felicitous events; and thus, when hearing a sneeze, will declare such responses as *Sante* or *gesundheit*, *Reichtum*, *ola*, *Dieu te, dominus tecum*; and for the pragmatic Dutch, *morgen mooi weer* (nice weather tomorrow).



This photograph captured a sneeze in progress, revealing the plume of salivary droplets as they are expelled in a large cone-shaped array from this man’s open mouth, thereby, dramatically illustrating the reason one needs to cover his/her mouth when coughing, or sneezing, in order to protect others from germ exposure.

CDC/JAMES GATHANY

Other cultures, more cautious about their futures, may utter: May God forgive you (Amharic), All Praise for Allah (Arabic), May good happenings arise (Assamese), May Jupiter preserve you (Latin), A fortunate occurrence (Cantonese), May you live long (Nepali), May you recover (Lugandese), and May it go right (Irish.)

Since a sneeze renders the soul of the sneezer to be transiently vulnerable, some responses are designed to create a temporary shield against impending evil. In some parts of Europe there is the further belief that one's heart stops momentarily during the sneeze; and this belief reinforces yet further the compulsion to bless the sneezer. Accordingly, no culture is without its rituals of sneeze-response. And with the possible exception of a rare anchorite meditating in some remote cave, a sneeze anywhere in the world will elicit an immediate response even from neighboring strangers. (The sneezes associated with seasonal release of goldenrod pollen have not yet infiltrated the texts of mythology.)

Modern physicians, too busy to study the mythic roots of sneezing, have determined that a proneness to sneezing might be an inheritable trait, particularly so when people with this genetic variant are suddenly exposed to bright sunlight (helio-ophthalmic outburst syndrome). Yet other humans are burdened by paroxysms of sneezing after an unduly heavy meal (for want of a better name, this is called The Achoo Syndrome). And finally there

are the sneezing-prone neuroses, amongst adolescents, that respond favorably to psychotherapy.

The secular advances of modern medicine have diminished the value of sneeze-generated responses. And so, when a person now sneezes in public, two societal responses become apparent: People will studiously ignore the event; or alternatively, someone will chastise the sneezer, accusing him of willfully contaminating the atmosphere with exotic viruses.

With all the perils assigned to sneezes – including cardiac arrest and the loss of one's soul – some sneezes persist in their innocence. There is, for example, A.A.Milne (1882–1956) and his clinical observations on the upper respiratory activities of Christopher Robin:

*Christopher Robin
Had wheezles
And sneezles...*

And then there is the earnest advice given by The Duchess in *Alice's Adventures in Wonderland* by Lewis Carroll (1832–1898):

*Speak roughly to your little boy,
And beat him when he sneezes;
He only does it to annoy,
Because he knows it teases. ❖*



Original illustration by John Tenniel (1914) in *Alice's Adventures in Wonderland*.

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