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Editorial

COV-19, Serendipity, and *Strange Interlude*: *Gloria in absurdicum* with an apology to Ovid

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The absurd edicts initially issued by several governors, including those of Michigan¹ and New York², prohibiting physicians from ordering hydroxychloroquine for patients suspected of or diagnosed with COV-19 are reprehensible. Their reasoning is beyond the pale.²

Hydroxychloroquine was first approved by the FDA in 1955 and has a remarkable safety record in its use as a preventative for malaria and in the treatment of several immunologic and/or light induced diseases. Its use came about serendipitously, and its mechanism of action is unclear, but the fact remains that it seems to work.^{3 4}

Strange Interlude

Why discuss Eugene O'Neil five-hour long soliloquy *Strange Interlude*?⁵ Although the play won the 1928 Pulitzer Prize for the best drama, the mayor of Boston banned it for its immorality.⁶ Consequently, the Theatre Guild moved the production to nearby Quincy. The drama was five hours long with intermissions so that audience could have refreshments. They soon discovered Howard Johnson's ice cream.⁷ Johnson (1897-1972) who became famous for his roadside restaurants and 28 flavors of ice cream was propelled in business by the moralist actions of a rigid big city mayor.

Serendipity Becomes a Hero

Many diseases are treated with medications for which they were not originally intended. Others have become an agent of choice and even the preferred one, but this requires the use of serendipity and in reality, trial and error.

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The word serendipity comes from Horace Walpole's writings about a fairy tale, *The Three Princes of Serendip*, who made very sensible, but accidental discoveries.⁸ This has occurred many times in medicine.⁹

The biologics, originally investigated for treating such diseases as psoriasis, are now used in correcting defects occurring in patients with genodermatosis. Ustekinumab, explored for treating psoriasis, is such a monoclonal antibody that may correct the genetic defect in ichthyosis. Simvastatin lowers cholesterol but used topically can be effective in treating the porokeratoses.¹⁰ Propanolol, as a beta-blocker, treats hypertension, but both orally and topically destroys hemangiomas.

Acne may be a disease from antiquity. No less an authority than Paul Gerson Unna (1850-1929) and others thought acne was a bacterial disease. Fast forward to the 1950's and the introduction of the tetracyclines for treating acne.¹¹ They work but the explanation remains as vague as when they were introduced. Does that suggest they should not be used, regardless of the question of bacterial resistance?¹²

We recognize that a randomized, double blinded (or sometimes even triple blinded) controlled trial is the gold standard for assessment of drug efficacy, but this may be impractical or even impossible in the real world of clinical practice. Alternatively, such trials may simply have not yet to be carried out at the time a physician needs to prescribe these medicines or treatments. In addition, such trials have numerous limitations of their own.¹¹⁻¹³

The present situation, in which physicians often prescribe treatments or medications "off label" as noted above, creates its own absurdities. We have witnessed government officials suppressing advertising of certain drugs for such off-label applications. May not this obstruct dissemination of useful clinical information, thus negatively impacting patient care? Is this really the best use of the officials' time and effort? Are not the care providers or drug company representatives harassed unnecessarily?

If a drug is FDA approved to treat patients with disease A, but it is primarily used to treat those with disease B, what happens if a better treatment emerges to treat disease A? What about patients with disease B, should approval of the drug be revoked? Is their health care not unnecessarily impeded? Alas, serendipity becomes a hero.

Conclusions

In a perfect world, every infectious disease would fulfil Koch's four postulates: ¹³

1. the pathogen must be present all of the time
2. the pathogen can be isolated from the patient
3. the pathogen can be cultured
4. the pathogen from the culture can cause the disease in an appropriate laboratory animal

And every treatment of every disease would be based on perfect randomized, double, or triple blinded studies. But this is not a perfect world. Physicians and scientists must be permitted the luxury of educated guessing; that is, serendipitous discovery without ill-informed interference. ¹⁴

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