STIMULATE THE PHAGOCYTES!

Immunology, as we know it, began during the 1880s when Russian zoologist Elie Metchnikoff described what he called “phagocytosis”, a process whereby white blood cells engulf and break down harmful pathogens. In 1908 Metchnikoff co-shared the Nobel Prize in Physiology and Medicine with the German chemist Paul Ehrlich “in recognition of their work on immunity.”.

Elie Metchnikoff was born in the Ukraine in 1845, the son of an officer in the Imperial Guard and a doting mother whose own father had converted from Judaism to Lutheranism. While pursuing a career in biologic research, he became obsessed with the process of digestion and how one cell “eats” another as a curative response to invading organisms. After resigning his position at the University of Odessa because of czarist ordinances that frustrated his work, Metchnikoff opened a private laboratory in Messina (Sicily) where he refined his theory until in 1888 he accepted an invitation from Louis Pasteur to join his new Institute in Paris where he could “properly pursue science.”

Metchnikoff’s theory, which came to be known as “cellular immunity,” did not involve antibodies. As he understood it, the body’s defense system involved an active process that engages various phagocytic cells (neutrophils, macrophages, monocytes, mast cells, cytotoxic T-lymphocytes.) In time he acknowledged the stimulatory effect of sensitized (opsonized) serum on phagocytes that enabled a more robust reaction. Paul Ehrlich’s approach, which emphasized the role of antibodies that could be quantified in serum, was called “humoral immunity” and although the two theories were not complementary, in the end both turned out to be correct. Perhaps Elie Metchnikoff achieved his greatest fame, however, for something very different.

Attempts to achieve longevity have a long history and among the most long lasting was the craze for yogurt that Metchnikoff set off in 1904 in a public lecture that simply was titled “Old Age.” In it he stated that aging was caused by harmful bacteria in the gut and his audience was urged to boil fruits and vegetables and otherwise prevent noxious bacteria from entering the body. Conversely, he suggested that beneficial bacteria need to be cultivated in the intestines and that this was best done by eating yogurt or other types of sour milk that contained the bacteria *Lactobacillus bulgaricu.* As he wrote, “Interestingly, this microbe is found in the sour milk consumed in large amounts by the Bulgarians in a region well-known for the longevity of its citizens. There is therefore reason to suppose that introducing Bulgarian sour milk

into the diet can reduce the harmful effect of the intestinal flora." Professor Metchnikoff suggested that if science found a way to "cure" aging, that people could live 150 years. Indeed Metchnikoff is sometimes credited as having coined the term "gerontology" in 1903.

Although Metchnikoff presented his ideas as a hypothesis, the next day Paris newspapers ran with the idea; *Le Temps* wrote, "Those of you pretty ladies and brilliant gentleman who don't want to age or die, here's the precious recipe: eat yahhourt." In the United States a headline in the *Chicago Daily Tribune* declared "Sour Milk is Elixir: Secret of Long Life Discovered by Prof. Metchnikoff." *The British Medical Journal* wrote, "Yoghourt can be used for an indefinite time without harmful results if the dose is not too large, 2.2 pounds a day should not customarily be exceeded." To counter sensational claims, the professor published a brochure in 1905 in which he wrote, "Clearly we do not look upon the milk microbes as an elixir of longevity or a remedy against aging. The question will be resolved only in a more or less distant future."

After Elie Metchnikoff shared the Nobel Prize with Paul Ehrlich, an article in the *New England Journal of Medicine* noted that now "everybody….has been taking Metchnikoff's milk with a fervor proportionate to the scientific authority of its promoter." This set off a mania for buying pots of yogurt and doctors began prescribing "Oriental curdled milk" for anything from gonorrhea to gum disease.

One acolyte was Dr. John Harvey Kellogg, of Cornflakes fame who, when he visited Metchnikoff in Paris, was impressed by the pitcher of sour milk that he saw on the professor's desk. In his own book, Kellogg wrote that Metchnikoff has "placed the whole world under obligation to him in his discovery that the flora of the human intestine needs changing." Dr. Kellogg had his own unconventional ideas about what kind of change. Since almost all illness originated in bowels as well as the stomach, he counseled daily yogurt enemas to produce sparkling clean intestines. Virtually all other disease was caused by sexual intercourse.

With his brother Will Keith Kellogg, John Harvey ran a fashionable sanitarium in Battle Creek, Michigan where wealthy neurotics were offered a vegetarian diet, exercise and sexual abstinence. This spartan regimen could best be summarized, if it feels good, it's bad for you. Kellogg theorized that these healthy bacteria helped digestion and improved the phagocytic capability of white blood cells — today's

probiotics. To test the benefits of consuming lactobacilli, he drank sour milk every day until he died at the ripe age of 71 years in 1916.

George Bernard Shaw was a satirist and socialist polemicist who won the Nobel Prize for Literature in 1925. He facetiously classified his play *The Doctor's Dilemma* as a tragedy, but it really was a comedy, the humour of which was directed at the medical profession. Shaw was a severe critic of medical hypocrisy, inequities of private practice and rationing of scarce resources. When *The Doctor's Dilemma* was first staged in London in 1906, it concerned the conflicts between the demands of the business side of private medical practice and the moral obligations of the profession.

In one memorable scene, a group of doctors gather to congratulate their colleague Dr. Colenso Ridgeon who has just been knighted for his success in treating tubercular patients whom he inoculated with an injectable antitoxin. Sir Ridgeon boasts that by sending "a drop of blood" to the hospital laboratory within fifteen minutes, he could establish a numerical "opsonin index" that indicated when it was safe to inoculate: "That's my discovery: the most important that has been made since Harvey discovered the circulation of blood. My tuberculosis patients don't die now….To inject a vaccine into a patient without first testing his opsonin is as near murder as a respectable practitioner can get."

As the doctors continue to engage in shop talk. Sir Ridgeon declares that the key to successful phagocytosis is to "butter the disease germs with opsonin to make your white blood corpuscles eat them."The metaphor was apt because the word "opsonin" was derived from the Greek opsōneîn, meaning "I prepare victuals for." As Metchnikoff understood the process, in a healthy individual to represent certain molecules mark dead and dying cells for clearance by macrophages and neutrophils and, continuing the digestive metaphor, opsonins cause the phagocytes to relish the tasty invader. What follows next is a portion of Shaw's script for *The Doctor's Dilemma* that discusses the nature of phagocytosis:

> Sir Patrick Cullen (a much older physician):"*That's not new. I've heard the notion of white corpuscles…what's his name, Metchnikoff calls them?*
>
> Ridgeon: *Phagocytes.*
>
> Sir Patrick: *Aye phagocytes: yes, yes, yes. Well I heard this theory that the phagocytes eat up the disease germs years ago: long before you*

came into fashion. Besides they don't always eat them….I've tried these modern inoculations a bit myself. I've killed people with them; and I've cured people with them; but I gave them up because I never could tell which I was going to do.

Ridgeon: *They [get better] when you butter them with opsonin….What it comes to in practice is this. The phagocytes won't eat the microbes unless the microbes are nicely buttered for them. The patient manufactures the butter for himself all right; but my discovery is that the manufacture of that butter, which I call opsonin, goes on in the system by ups and downs - Nature always being rhythmical, you know. What the inoculation does is to stimulate the ups or downs as the case may be….Everything depends on your inoculating at the right moment. Inoculate when your patient is in the negative phase, the downgrade, and you kill: inoculate when the patient is in the positive phase, up-grade, and you cure.*

Sir Ralph Bloomfield Bonington who partially agrees with Sir Ridgeon, according to GBS, "is known in the medical world as B.B. and the envy roused by his success in practice is softened by the conviction that he is scientifically considered a colossal humbug."

B.B.: *Nature has provided the white corpuscles as you call them — the phagocytes as we call them — a natural means of devouring and destroying all disease germs. There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes. Drugs are a delusion. Find the germ of the disease; prepare from it a suitable anti-toxin; inject it three times a day quarter of an hour before meals; and what is the result? The phagocytes are stimulated; they devour the disease' and the patient recovers - unless, of course, he's too far gone….Everything is dangerous unless you take it at the right time. An apple at breakfast does you good: an apple at bedtime upsets you for a week.*

In the play, Sir Colenso Ridgeon was a caricature of Shaw's real-life friend Sir Almroth Wright (1861-1947), a biologist who had developed the first successful vaccine against typhoid. A historian once described Wright as "a romantic who only accepted those pieces of science that suited him." Some critics referred to him as "Sir

Almost Wright" — others called him "Sir Always Wrong." In 1911 Shaw added a lengthy preface to *The Doctor's Dilemma* in which he explained why he invented Sir Colenso Ridgeon to serve as his friend's fictional alter ego:

Sir Almroth Wright, following up one of Metchnikoff's most suggestive biological romances, discovered [in 1902] that the white corpuscles or phagocytes attack and devour the disease germs, appetizingly for them with a natural sauce which Sir Almroth named opsonin, and that our production of this condiment continually rises and falls rhythmically from negligibility to the highest efficiency…By the time this preface is in print…opsonin may have gone the way of phlogiston.

But economic, societal and political considerations notwithstanding, science can't be rushed. I suspect that were Shaw's fictional doctors around today, they would advise their modern counterparts to *STIMULATE THE PHAGOCYTES!* And if so, they might have been correct.