

Serotherapy for Ebola: Back to the Future

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In dramatic, front-page news, Kent Brantly and Nancy Writebol, 2 American missionary workers infected with the deadly Ebola virus, were given a “highly experimental” combination of preformed monoclonal antibodies directed against the virus and previously shown to work only in monkeys. Brantly, moribund and poorly responsive to a previous blood transfusion containing convalescent antibodies, apparently began to recover “within an hour of receiving the medication . . . [and] was able to take a shower on his own before getting on a specially designed Gulfstream air ambulance jet to be evacuated to the United States” (1).

This is not the first time that passive serotherapy has been described as “miraculous.” These headlines hearken back to well over a century ago, decades before the advent of such miracle drugs as sulfonamides and antibiotics. Medical scientists and practitioners did not wait for such unknown drugs. Rather, if the 1870s and 1880s represented the golden age of microbiology, as Louis Pasteur and Robert Koch led in identifying the agents of anthrax, diphtheria, pneumonia, tuberculosis, and the like, then the 1880s and 1890s represented the advent of applied humoral immunology. By 1890, Emil von Behring and Shibasaburo Kitasato, working under Koch in Berlin, had identified humoral factors in exposed animals that when transferred into laboratory animals were protective against diphtheria and tetanus toxins. From the 1890s onward, this model of production—expose an animal (such as guinea pig, rabbit, cow, or horse) to an identified microbial pathogen, generate antibodies (or use convalescent serum from former patients), and then “passively” transfer the preformed antibodies to an exposed animal or person—could be expanded to such feared and prevalent diseases as pneumococcal pneumonia and meningococcal meningitis.

This was scientific medicine at its most precise. When Paul Ehrlich coined the term “magic bullet” in 1906, he was in fact referring to such precision antibodies, to which chemotherapy could only aspire (2). The antiserum treatment of pneumococcal pneumonia from the 1910s through the 1940s is perhaps the most instructive for our purposes (3). The Hospital of the Rockefeller Institute was opened in 1910 to serve as a model of bench-to-bedside medicine. Its first director, Rufus Cole, had gathered a team that included Oswald Avery and demonstrated through case series of patients that if pneumococci were divided into serotypes, then type-specific antipneumococcal serotherapy could dramatically reduce deaths from certain key strains of the “captain of the men of death.” Cole planned to test the remedy in careful fashion among

encamped soldiers gathering for World War I, but the chaos of the 1918 influenza epidemic threw such plans into disarray.

The Metropolitan Life Insurance Company lost \$23 million in excess death benefits during the epidemic. In response, it funded a series of studies at multiple institutions—Bellevue Hospital, Boston City Hospital, and Harlem Hospital—to test the efficacy of the remedy by a method that went beyond the case study: controlled studies, in which every other patient (or patients on every other ward) received serotherapy, with results tabulated and statistically compared (and in some cases tested for statistical significance). Serotherapy was demonstrated to be effective against certain serotypes in the hospital setting, with once-moribund patients described as sitting in their beds reading the newspaper the following morning, reminiscent of Kent Brantly’s recovery (4).

Serotherapy was found most effective when administered early (again analogous to the treatment of Ebola, it seems), but most patients did not make it to the hospital in time to receive the remedy early in the course of the disease. In the setting of this apparent delivery gap, the Massachusetts State Board of Health originated the first pneumonia control program, through which pneumococcal “typing” stations and serum depot centers were established across the state, available to assist local practitioners so they could administer antiserum in the home. By the late 1930s, Surgeon General Thomas Parran declared a “war on pneumonia,” framing it around the notion of health as a fundamental right and the equitable distribution of the expensive and logistically complicated antiserum as a test of the advancement of the nation. Federal funding assisted the formation of pneumonia control programs in approximately two thirds of the states across the country.

But with the advent of effective antipneumococcal sulfa drugs in the late 1930s and then penicillin during World War II, the pneumonia control programs collapsed entirely, as the antibiotic era gave rise to a new optimism—some would say “antibiotic abandon”—and dreams of the conquest of all infectious disease (5). Antibiotics transformed the very practice of medicine, at the same time that they shaped the marketing and even the regulation of pharmaceuticals by the U.S. Food and Drug Administration more broadly from the 1950s onward (6, 7). By the late 1980s and early 1990s, however, in the wake of the AIDS

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epidemic, increasingly identified antibiotic resistance, public health retrenchment, and increasing globalization, such initial optimism had given way to fears regarding “emerging infections” and a “world out of balance” (8). Today, nearly half a century after the first evocation of a microbial “superbug” (9), we are surrounded by ever-escalating concerns regarding a “postantibiotic era” and emerging pathogens.

We have long expected science to rescue us from microbial pathogens, and the monoclonal antibodies that seem to have cured Kent Brantly are indeed miracle cures. Monoclonal antibodies themselves were not created until decades after the collapse of the last pneumonia control program, and modern science may well redefine research into a host of antimicrobial remedies, including bacteriophage therapy, probiotics, and passive serotherapy, that have their origins in the preantibiotic era.

However, we can draw still further lessons from the earlier era of passive serotherapy. How can we ensure that such new magic bullets get to patients who need them, when and where they need them? How can this be done in an equitable fashion? And who gets sick in the first place, and why? There is only so much we can ask of seemingly magic bullets alone (10).

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References

1. Gupta S, Dellorto D. Experimental drug likely saved Ebola patients. CNN.com. 4 August 2014. Accessed at www.cnn.com/2014/08/04/health/experimental-ebola-serum/index.html on 4 August 2014.
2. Ehrlich P. Address delivered at the dedication of the Georg-Speyer-Haus. In: Himmelweit F, ed. *The Collected Papers of Paul Ehrlich*. vol III. New York: Pergamon Pr; 1960:53-63.
3. Podolsky SH. *Pneumonia Before Antibiotics: Therapeutic Evolution and Evaluation in Twentieth-Century America*. Baltimore: Johns Hopkins Univ Pr; 2006.
4. Dowling HF. The rapid diagnosis and serum treatment of lobar pneumonia. *Med Ann Dist Columbia*. 1935;4:66-70.
5. Whorton J. ‘Antibiotic abandon’: the resurgence of therapeutic rationalism. In: Parascandola J, ed. *The History of Antibiotics: A Symposium*. Madison: American Institute of the History of Pharmacy; 1980:125-36.
6. Bud R. *Penicillin: Triumph and Tragedy*. New York: Oxford Univ Pr; 2007.
7. Podolsky SH. Antibiotics and the social history of the controlled clinical trial, 1950-1970. *J Hist Med Allied Sci*. 2010;65:327-67. [PMID: 20215414] doi: 10.1093/jhmas/jrq003
8. Garrett L. *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*. New York: Farrar, Straus & Giroux; 1994.
9. Osmundsen JA. Are germs winning the war against people? *Look*. 18 October 1966:140-1.
10. Brandt AM. *No Magic Bullet: A Social History of Venereal Disease in the United States Since 1880*. New York: Oxford Univ Pr; 1985.

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