

Mini Review

Antimicrobials, chemotherapeutics or antibiotics?

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Accepted 15 August, 2011

Antimicrobials are the broad classes of substances acting against microorganisms. As there is a need for stability and consistency within Science, this must also be applied to the business of defining the different categories of antimicrobials correctly. This is of special importance, since various compounds known for activities outside this field of interest are now also surfacing as antimicrobials.

Key words: Antibiotics, anticancer, anti-inflammatory, antimicrobials, chemotherapeutics, definitions.

INTRODUCTION

What exactly are antimicrobials? What is meant by chemotherapy and antimicrobial chemotherapy? and where do antibiotics fit into the picture?

Mention the word "chemotherapy" and one immediately thinks of cancer. However, chemotherapy for anticancer purposes was first successfully used only in 1946 (Hirsch, 2006), some four decades after the development of Paul Ehrlich's first chemotherapeutic drug Salvarsan, which was used for antimicrobial purposes. So chemotherapy, in the original sense of the word, was not at all used in connection with cancer; it was used to describe chemical substances that had a killing effect on bacteria, that is microbes. It should be noted that Ehrlich himself showed an interest in treatment of cancer with drugs (DeVita and Chu, 2008), but he did not have high hopes that this would be possible. Apparently, he had a sign on his laboratory door where he did this research that read "Give up all hope oh ye who enter" - amusing, in the light of the knowledge about anticancer drugs that we have today.

Also, as part of antimicrobials (Figure 1) we have the antibiotics. These have been in use for thousands of years to treat wounds and infections (Duckett, 1999), but it was not until the 20th century that the impact of antibiotic substances was realized. Antibiotics stand in contrast to chemotherapeutic agents as they are of

natural origin, whereas chemotherapeutics are synthetic. The potential of antibiotics in anticancer chemotherapy was investigated in the 1950s (DeVita and Chu, 2008) and positive results arose from this research. Antibiotics and antibacterial chemotherapy developed separately and can therefore be considered to be two distinct, separate classes of antimicrobial therapy. But in what light is this seen today? In general, microbiology textbooks define the word "antimicrobial" as being "harmful to microorganisms by either killing or inhibiting growth". Likewise, an "antimicrobial agent" is "a chemical that kills or inhibits the growth of microorganisms". Quite acceptable definitions and this also applies to "antibiotic", which they define as "a chemical substance produced by a microorganism that kills or inhibits the growth of another microorganism" (Madigan et al., 2009).

However, when it comes to the definitions of "chemotherapy" and "chemotherapeutic agent", confusion arises. These two terms are many times defined as, respectively, "treatment of infectious disease with chemicals or antibiotics" and "an antimicrobial agent that can be used internally" (Madigan et al., 2009). This confusion is also widely published on the Internet today (e.g. <http://en.wikipedia.org/wiki/Chemotherapy>). Paul Ehrlich, who was the first person to use the term "chemotherapy" had a different definition for this word than the one in general acceptance today. Ehrlich's idea of chemotherapy was "the use of chemical substances, especially those produced synthetically, to destroy pathogenic microorganisms within the body" (Parascandola, 1981). Note how this definition states "produced synthetically". Does that include antibiotics,

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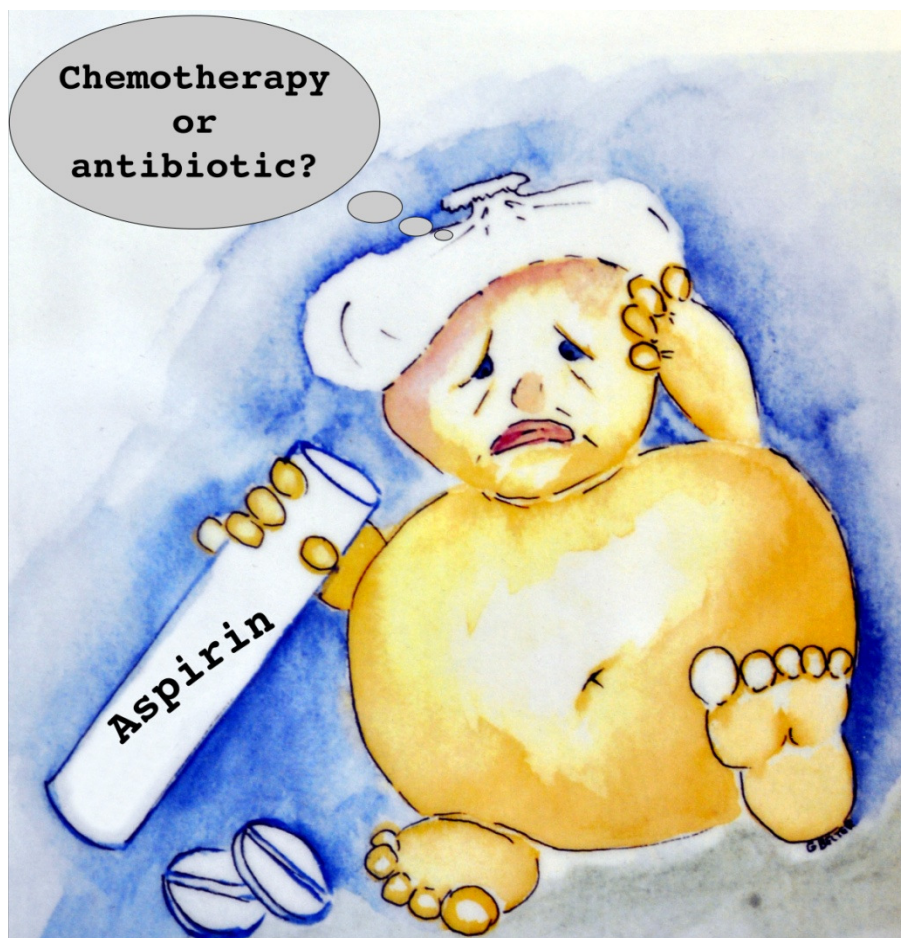


Figure 1. “One confused microorganism.” Adapted with permission from Kock et al. (2005).

which are chemicals of natural origin, as is incorporated into many microbiology textbooks? Ehrlich’s precise words regarding his work were the following:

“...we [are]... concerned with the problem of curing organisms infected by certain parasites... by the use of substances which have had their origin in the chemist’s retort”.

Again, this implies that for any substance to qualify as a chemotherapeutic agent, it “must be produced synthetically”. This argument is supported by literature aging from the advent of antibiotics. Selman A. Waksman, who in 1952 won the Nobel Prize in Physiology or Medicine for his discovery of the first effective antibiotic against tuberculosis, namely streptomycin, had some part to play in the struggle, so to say, of correctly defining antimicrobials. In a 1942 article, he suggested that a new definition would be required under which penicillin and other similar substances would fall, as it was apparent that these could not be classified

alongside chemotherapeutic agents (Waksman, 1947). He put forward the terms “antibiotic” and “antibiotic agent”. He defined an “antibiotic” as “inhibiting the growth or the metabolic activities of bacteria and other microorganisms by a chemical substance of natural origin”, and the definition for an “antibiotic substance” was “a chemical substance, of microbial origin, that possesses antibiotic properties”. It is possible that Waksman derived his terms from that of Jean-Paul Vuillemin, who in 1889 first described the killing of one organism by another for purpose of survival as “antibiosis” (Lax, 2004).

In later literature, the disorder that Waksman tried to eliminate crept back in. It is not at all uncommon to read articles where antibiotics are referred to as chemotherapeutic agents and where the term chemotherapy is used in such a way as to include anything having an antimicrobial effect. Should this not be an important issue, as it most definitely has an effect on the international science community’s understanding of the subject? For instance, if a scientist in Japan

speaks of a chemotherapeutic agent, one in South Africa might think of an antibiotic. Or if a scientist from Britain presents research on some kind of new antibiotic-producing organism, some of those across the world reading his work might regard it as a breakthrough in the field of chemotherapy. The impact of this mishandling of terms is clear, and is relevant also when practically applied. An example is in hospital environments – one doctor speaks of treating a certain patient with antibiotics; another misunderstands this and begins administering chemotherapeutic drugs to the patient in question. Potential fatal results? This might not be a very probable scenario; the point, nevertheless, is that if clear limits for definitions are not recognized, there will be a lot of confusion that could otherwise have been avoided. Besides this, is of course also the issue of being historically correct in applying definitions in light of the development of antimicrobials as discussed.

Now another problem emerges. What about the synthetically modified antibiotics that have made their appearance some years after large-scale production of antibiotics started (Rolinson, 1979)? Into which category do they fall? They are not fully synthetic, as they are still produced by microorganisms, and yet they are not 100% natural, as they have been chemically modified in the laboratory. Are they then antibiotics or are they chemotherapeutic drugs? Or should they fall into an entirely new class and accordingly also be defined anew? Rolinson stated the following in 1979:

"Another approach to the preparation of compounds not otherwise available as naturally-occurring substances is the chemical modification of penicillins which can themselves be obtained by fermentation. Penicillins prepared in this way can thus be said to be semisynthetic."

It is reasonable that this will then also apply to any other antibiotic that has been chemically modified. The suggestion is to have three categories under the class of Antimicrobials: (1) the chemotherapeutics, as defined by Paul Ehrlich; (2) the antibiotics according to the definition by Selman Waksman and (3) the semisynthetics referred to by Rolinson in his article.

It is interesting to note that evidence is starting to surface that chemotherapeutic anticancer drugs such as Lonidamine also have potent antifungal activity (Kock et al., 2009). It should as well be pointed out that, by taking the endosymbiotic theory into account, chemotherapeutic

anticancer drugs targeting mitochondria may also be effective against certain bacteria, e.g. the *Rickettsia* (Lang et al., 1999; Gray et al., 2001). To complicate things further, the non-steroidal anti-inflammatory drug, aspirin, has recently been shown to not only have antimicrobial but also anticancer activity (Davis et al., 2009; Kock et al., 2007, 2009; Rothwell et al., 2011). Can aspirin therefore be regarded as chemotherapeutic: anti-inflammatory, antimicrobial as well as anticancer?

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