EVIDENCE BASED MEDICINE AND THE TREATMENT OF THE PATIENT WITH CANCER

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When we strategize the "best" treatment for any given patient, we do so, ideally, by applying principles of Evidence Based Medicine (EBM). EBM has been described as "the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients."[1] This can be interpreted in two ways. Modern medicine has interpreted this to mean the application of a clinical treatment protocol based upon the statistically best outcome of randomized controlled studies for that diagnosis which it refers to as the "standard of care". Unfortunately, if the "war on cancer" has taught us anything it is that treating the individual based upon population statistics doesn't work well for long term responses.

Historically, there are four identified periods of EBM[2]. The **Ancient period** was characterized as a time of authority based upon experience and apprenticeship with a smattering of anecdotal "old wives tales" and information handed down to us by the "Gods and spirits of nature". Here, the high priests of the Druids leap to mind as an example of such knowledge. Next came the **Enlightenment period** which began in about 1700. During this time there was growing skepticism about authority figures and this lead to the development of the first recorded clinical trials (Cataract treatment trial in Hospital Royal des Invalides, Paris 1757) and medical information accumulated in the form of literature reviews. One important example of this is the 1753 book by Dr. James Lind "Treatise of the Scurvy". This book contained a detailed systematic review of everything that had been written about Scurvy, a nutritional deficiency "disease" that was killing thousands of people every year. It also contained a comparison of the different medical treatments that were available at the time to treat this affliction. The early 1900's began the **Transitional period**. Here the standard of measure was the "end result" of any given treatment and thus was later born the randomized clinical trial. Credit for conducting the first pharmaceutical randomized clinical trial (RCT) is most often given to Sir Austin Bradford Hill for his work in the late 1940s on the United Kingdom Medical Research Council's trial of the effects of the aminoglycoside antibiotic streptomycin on tuberculosis, which became the first antibiotic treatment for this disease. Now, we are in the "**Modern period**" where not only do we use RTC's, based upon a ridiculous "magic bullet" approach, but also evaluative science to do "data mining" from past trials and "MetaDrug analysis" to predict safety and efficacy.

The current “Modern period” recognizes the need to integrate 3 disparate bodies of information to find the “best” treatment for any individual, but rarely actually does it[3]. First comes the patient’s values and beliefs. If the patient ONLY believes in, and will accept, treatment from the local Shaman then that will limit their treatment options, as it will if they were a Jehovah’s Witness. Next we have the Clinical Experience of the practitioner and the availability of specialized medicines and/or technologies. Take a top cardio-thoracic surgeon and drop her into the middle of the Amazon jungle, under those circumstances there is little that she can do for a patient there who needs a heart transplant. Finally, we come to the third component which is that of the Scientific Evidence itself. Without digressing tangentially into a discussion of how one, on a personal basis, accepts what is scientifically true (Thomas Kuhn[4] and Karl Popper[5] not withstanding) let me just say that there are endless discussions on the validity of scientific studies in the medical literature. The scientific literature is currently based upon non-individualized population statistics, which has very little direct relevance to the individual and results in what is referred to as Clinical Evidence (CE) . In a nutshell, for (CE) we summarize the current state of knowledge - and uncertainty - about interventions used to prevent and treat important clinical conditions. We do it by searching and appraising the literature to create rigorous systematic reviews of evidence on the benefits and harms of clinical interventions. When ideally applied EBM is not "cookbook" medicine. Because it requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patients' choice, it cannot result in slavish, cookbook approaches to individual patient care. External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision. Similarly, any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether or not it should be applied. “Objectively” collating external evidence results in a hierarchy of what is likely to be most appropriate for any given patient at the present time. The sources of external evidence include: Cohort Studies, Randomized Clinical Trials (RCT’s), Systematic Reviews (Data mining), Case studies and Mechanistic Reasoning (MetaDrug analysis) and point in the direction of potential treatments. These potential interventions are further organized into six “effectiveness” categories[6]:

Intervention	Icon	Description
Beneficial		For which effectiveness has been demonstrated by clear evidence from systematic reviews, RCTs, or the best alternative source of information, and for which expectation of harms is small compared with the benefits.
Likely to be beneficial		For which effectiveness is less well established than for those listed under "beneficial".
Trade off between benefits and harms		For which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.
Unknown effectiveness		For which there are currently insufficient data or data of inadequate quality.
Unlikely to be beneficial		For which lack of effectiveness is less well established than for those listed under "likely to be ineffective or harmful".
Likely to be ineffective or harmful		For which ineffectiveness or associated harm has been demonstrated by clear evidence.

The "best" balance of these elements is decided upon, non-linearly, intuitively (Michael Polanyi[7]), by the individual physician thus leaving room for a different interpretation by another physician which we call a second opinion. The point of all of this is that **there are NO statistics for the individual patient**. The physician has to set his/her own threshold, based upon their experience, of when there is enough of the right type of evidence for them to recommend and proceed with a specific treatment. There are no guarantees, only outcomes. Based upon known pathophysiology, we know what will likely happen if we do nothing. So we recommend a course of therapy and then monitor the clinical response closely with blood tests and imaging of various sorts. If what we're doing is working, within the time frame that we expect, and that criteria must be individually set as well, then don't mess with it, rule number one. If it's not working, then do something else. Essentially, we have a closely monitored clinical trial with an "n" of 1.

To escape from the barely relevant realm of population statistics we personalize patient care by individualizing every level of treatment through the use of extensive laboratory testing. We **first** start by asking not what kind of cancer a patient has (the diagnosis is only relevant to population statistics) but rather what are their cancer cells sensitive to? Given the myriad of genetic defects that plague (cause and/or perpetuate) cancer cells each persons cancer will have slightly different abnormalities that give their tumor an individualized response to the chemotherapeutic agents. This information is collected through either direct cell culture sensitivity testing (Rational Therapeutics[8]) or indirect, inferred testing based upon the genetic abnormalities identified (Caris[9]). By more specifically targeting the cancer cells with Insulin (IPT) we can use much lower doses of the drugs that have been identified as being useful and have a rapid responses to therapy, with a minimum of toxicity[10].

Second, we do a set of blood tests that look at what is going on biochemically. Here we are endeavoring to ascertain three things. First we want to know if the person has any absolute nutritional

deficiencies of vitamins, minerals, protein, fatty acids, what have you. An absolute nutritional deficiency is uncommon in the United States but a relative nutritional deficiency is not. Relative nutritional deficiencies occur when the person is eating the right foods and taking the right supplements but either they are burning them faster than they are pumping them in or, more commonly, they aren't absorbing them. As we age the amount of HCl that is produced by our stomach and enzymes, that are produced by our pancreas, steadily decreases. This results in an impaired capacity to digest food (break things down into their component parts) and then absorb them. Tests like a Heidelberg capsule test can quantify this[11]. Next we want to get a sense as to how toxic the individual is so that an appropriate level of detoxification can be implemented. Finally, we need to know what is going on with the balance of fatty acids. Fatty acids serve MANY vital biochemical functions. One important one is that they are incorporated into and make up the cell membrane. The balance of fatty acids will affect the structural integrity and flexibility of the cell membrane. This has a direct affect on the functional capacity of the receptor sites that are located on and through the cell membrane[12]. The Immune System consists of a relatively few specialized cells that communicate with each other with various information molecules including cytokines. For the cytokines to work they have to interact with the appropriate receptor site, on the cell membrane, thus allowing them to transmit their signal. In any case the results of these tests allow us to individualize our biochemical (diet, detox and supplementation) recommendations. Needless to say, this is CRITICAL because an effective immune counter attack is based upon an intact biochemistry.

The **third** leg of our therapeutic stool is that of evaluating and supporting the immune system and its response, or lack thereof. The immune system is critical in four areas. First it has the primary job of protecting us from developing a cancer to begin with[13]. Second, in early cases, before chemo has destroyed it, the immune system may be able, with the right kind of help, to stop and reverse the cancer by itself[14]. Third in more advanced cases Immunotherapy can be used with the right kind of Chemotherapy to synergistically destroy a tumor[15]. Finally, it is the job of the immune system to protect us from a recurrence once the cancer has been stopped[16].

As part of addressing the immune system we have to also look for toxins[17] that can suppress its function and psychodynamic factors that can suppress or support it. Some of these factors include; using process oriented psychotherapy to look at the beliefs and stressors of the patient, techniques of psychoneuroimmunology[18], meditation and the like.

The integration and application of these therapies, through the thinking of the post-modern world of integrative medicine, represents the highest application of the principles of evidence based medicine and, it is my opinion, provides the individual with the greatest opportunity for a maximum of quality and quantity of life.

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