

Immunomodulation – An Idea from the Past Looks More Promising Than Ever

In this issue of the *BJID* the case report by Badaró, *et al.* reminds us again of the potential for the human immune system to overcome pathogenic processes, assisted by some new ideas from the fields of biological science and medical care. Stimulation of the immune response to control disease is quite an ancient approach to medical care, side-tracked during the time of our fathers and grandfathers by the development of the magic bullet against microbial disease and cytotoxic chemotherapy against malignant processes. Over 100 years ago microorganisms were injected into patients in an attempt to cure malignant diseases [1], or to treat infections such as syphilis by inducing fever [2, 3]. The process of blood letting [4], modified in Brazil (as reported to me by Dr. Heonir Rocha) by re-injecting the removed blood subcutaneously, was certainly a potent form of cytokine stimulation. Other forms of non-specific immune or inflammation stimulants included heavy metals, such as arsenic or mercury [5], in ancient times, and, more recently, leukocyte products (transfer factor) [6], and mycobacteria [7]. The relative successes of these methods are difficult to determine in retrospect, because the science of clinical trials documentation was not yet mature, and because the efficacy of the approaches to antimicrobial therapy and cell-cycle specific chemotherapy were so dramatic, our attention was directed toward specific attack against the microbe or tumor cell. From many different areas we see that the magic bullet approach may no longer be enough. These areas include the emergence of multi-drug resistant organisms and the difficulty of controlling infection in immunologically suppressed patients after cancer chemotherapy or with HIV infection. The emergence of our knowledge of immunology has allowed the medical profession to re-explore these ancient ideas using new tools and with a fresh conceptual understanding [8].

The case presented in this issue of the *BJID* is particularly relevant to this history because it reminds the reader of the problems in patient care when antimicrobial agents are ineffective or too toxic, as

shown to be the case with both the use of amphotericin B and pentamidine. It is also relevant because attempts at general immune stimulation with a mixture of leishmanial antigens presently used in Brazil for immunotherapy [9] was only partially effective, reminding us that the immune system requires a carefully tailored approach. The case moves us into the future by the use of leishmanial antigens which were defined by using the most up-to-date methods, and by the selection among 15 antigens, 4 to which the patient was unresponsive, postulating that it is the mis-direction of the immune response, not its absence, that had led to the continued inflammatory process. It is also relevant that one of the antigens selected, LiEF, has been shown to be one of several leishmanial antigens which has Th1 stimulatory actions [10], to which a newly recognized immunomodulatory cytokine, GM-CSF, was added [11, 12]. The photographs tell the story – a desperate patient returned to a normal social existence.

Of course, now comes the cautionary note. This is one patient, not a controlled clinical trial, the antigen mixture has not been validated or registered, the role of each component has not been defined. Indeed, whether all of the components (leishmanial antigens, the special leishmanial antigen with adjuvant activity, and GM-CSF) are required is not known. It is my hope that by publishing this case, renewed interest in immunomodulation will be stimulated, and the commitment of time (years) and expense (millions of dollars) will be considered justified. If the result of the publication of this case is only an hysterical scramble to obtain the antigens and adjuvants for other patients, our goal has not been achieved. It is unfortunate, but a reality, that these antigens will not be available for several years to come. This case should stimulate further investment in creative research and thinking, not the obtaining of the specific materials used.

Immunomodulation using up-to-date methods has already become a reality [13]. For example, interferon gamma is used in patients with chronic granulomatous disease [14], interferon alpha is used in patients with

lymphoma [15] or chronic hepatitis C [16], IL-2 is used in patients with AIDS [17], and numerous vaccine adjuvants have been developed [18]. The case recorded here of the use of immunomodulation in a patient with mucosal leishmaniasis is an important contribution, by applying recent knowledge of immunology to an ancient method of treatment.

Thomas C. Jones

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