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Non-specific host defence stimulation in the reduction of surgical infection in man

Problems remain, with respect to the control of infection in surgical patients, more than 100 years after the seminal discoveries of Pasteur and Lister. Elective operations continue to carry a 5–7 per cent infection rate despite the wisest possible use of prophylactic antibiotics and optimum sterile technique. Similarly, badly hurt and contaminated patients ultimately manifest infection as the commonest cause of death in a particularly depressing final common pathway of multiple system organ failure. Furthermore, intraperitoneal sepsis remains an incompletely controlled process with a continuing high death rate, particularly in the elderly and in patients whose secondary peritonitis is diagnosed late. It is salutary to note that infection remains the commonest cause of death in the burn patient.

This state of affairs has stimulated many workers to re-examine the age-old proposition of non-specific stimulation of host defence processes. The latest re-emergence of this concept is less than two decades old, and many of the early measures were crude attempts to use agents such as BCG[1] and *Corynebacterium parvum*[2]. Each of those agents provided a degree of protection in highly controlled, carefully conducted experiments simulating surgical infection; the protection was modest and always associated with a reciprocal depression of host defence responses which was dose and/or time related. The discovery and ultimate synthesis of muramyl dipeptide, a defined component of the *Mycobacterium* cell wall, allowed direction of this non-specific stimulus[3]. It is quite clear from the studies of our colleagues at the Institut Pasteur[4] and from our own experience that muramyl dipeptide is a remarkably effective agent which accomplishes, experimentally, many desirable ends, remaining effective in the face of a variety of clinically significant immunodepressant manipulations[5,6]. Furthermore, the agent was shown to be effective, though to a lesser degree, when used for the first time after contamination, and also for polymicrobial sepsis[7,8]. Perhaps most importantly, it was shown to be effective when given in addition to both bacteriostatic and bactericidal antibiotics[9]. Given this remarkable sequence of clinical simulations, one may question why the agent has not moved to bedside trials. An initial clinical trial for the control of post-prostatectomy bacteriuria was promising but, ultimately, no benefit was demonstrated despite considerable concern about the likelihood of type II statistical errors. For whatever reason, the principal patent holder has chosen to focus on the very humane question of its use as an adjuvant to vaccines used for a variety of parasitic diseases in third world countries, and there is little likelihood that it will be promptly assessed for any innate but non-specific benefit in clinical surgery.

As in the elucidation of the ultimate cause of post-traumatic pulmonary insufficiency[10], we decided to turn back to the active trauma services at the University of Louisville Hospitals and begin to examine, in a descriptive and exploratory fashion, the host defence abnormalities in badly injured man. The results of these studies have been widely debated and have provoked several efforts to repeat them in laboratories around the world. Suffice it to say that detailed testing of badly injured man in our principal teaching hospital disclosed only two primary abnormalities that appeared to be independent variables[11]. The first was the capacity of the hosts' monocytes to present antigens appropriately for processing. This antigen-presenting activity was sharply depressed shortly after injury in patients destined to develop severe and frequently fatal infection; it remained depressed for long periods even in those patients ultimately likely to recover from infection. Indeed, recovery correlated very precisely with the return of this monocyte activity toward normal. The second independent variable identified and confirmed has been the tendency of patients' serum to show depressed ability to support phagocytosis by normal neutrophils. Indeed, both extremes of opsonization have been informative; some patients have recovered after repeated bacterial challenges, manifesting clear-cut evidence of a 'super serum' activity, while patients prone to progressive and/or fatal infection demonstrated

subnormal responses in terms of the capacity of their serum to opsonize test bacteria by normal neutrophils.

The monocyte abnormalities led to a bench pursuit of those methods likely to enhance them, and it is quite clear that *in vitro*, lipopolysaccharide (S. H. Appel, S. T. Wellhausen, M. J. Hershman and H. C. Polk Jr, unpublished data) is consistently capable of stimulating monocyte antigen-presenting activity into the normal range, parenthetically reinforcing the suspicion that under certain circumstances muramyl dipeptide, with its lipopolysaccharide-like activity, remains a highly promising therapeutic possibility. *In vitro* studies have also shown the consistent ability of interferon gamma (IFN-γ) to stimulate macrophage and monocyte activity (M. J. Hershman, S. H. Appel, S. T. Wellhausen, G. Sonnenfeld and H. C. Polk Jr, unpublished data). In a sequence of studies as yet unpublished, *in vivo* IFN-γ has shown consistent effectiveness in surgical models when used for prophylaxis and for therapy, and under conditions of polymicrobial bacterial sepsis. This protective effect in terms of degree of bacteraemia and, indeed, survival was constant and statistically significant but always small! The prospects for a clinical trial are at least dampened by the realization that such an undertaking in the face of only small benefits may well lead to falsely negative clinical results. In theory, the ideal application of this concept, which has a sound classical immunological basis, as well as a sound laboratory background, would be the sequential use of IFN-γ, muramyl dipeptide and possibly tumour necrosis factor[12], with the likelihood that there could be sustained enhancement of host defences until the septic challenge was overcome.

In any event, non-specific enhancement of host defences has been an active and rewarding field of inquiry; it is likely that some or many of the concepts generated will find their way to the bedside, assuming that the early experimental results can be repeated by other groups in a consistent fashion.

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