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Invited commentary on David Fedson's article

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The recent H5N1 and H1N1 scares demonstrate that political, bureaucratic, and to a large extent scientific, thinking about how to ward off potentially large fatalities is currently restricted to stockpiling antivirals and generating new vaccines. Nevertheless, as David Fedson pointed out with undeniable logic in last month's issue of this journal (3: 129–142), an influenza research community that continues to confine its efforts to these approaches will fall far short, in any severe pandemic, in its brief to prevent worldwide high mortality.

Central to Fedson's answer to this challenge is for us to examine more closely the argument that a fatal outcome in influenza is largely a manifestation of excessive release of inflammatory cytokines, as embodied in the cytokine concept of disease. Given reasonable acceptance of this, he argues, we should then put more effort into testing the potential for treating influenza illness with cheap and readily available agents that are already, on other rationales, in therapeutic use for other purposes, and also known to suppress production of disease-inducing cytokines.

What is the cytokine concept of disease, and how wide is its relevance across the infectious diseases? The idea began nearly 30 years ago when a newly described endogenous anti-tumour agent[1] was used to rationalise the nature of malaria and systemic bacterial infections.[2] As reviewed,[3] when rTNF was later being tested as an anti-tumour agent in patients, the toxicity that prevented its widespread use so strikingly mimicked influenza that tumour researchers referred, in print, to it generating influenza-like side effects.[4] Symptoms, which included fatigue, fever, anorexia, chills, headache, pulmonary oedema, immunosuppression, myalgia, nausea, vomiting and diarrhoea[5,6] were worse with higher doses. Parenteral interleukin-2, by inducing TNF, also produces a very similar clinical picture.[7]

Together with influenza being the standard misdiagnosis of imported malaria in temperate countries, the experiences of these tumour researchers made it plausible that this disease model would explain the pathology of viral diseases, including influenza, as well as that of malaria and bacterial sepsis.[8] The concept of cytokine excess has also been adopted to rationalise the diseases caused by *Mycobacterium* spp.,[9] *Salmonella typhi*,[10] *Leishmania* spp.,[11] *Toxoplasma gondii*,[12] *Coxiella brunetii*,[13] and *Listeria monocytogenes*.[14] It dominates the literature on the pathophysiological consequences of trauma, haemorrhagic shock, and burns because these, too, originate from cytokine excess.[15,16] Different triggers (gram-negative lipopolysaccharide, gram positive toxins, fungal or malarial toxins, or modulation of RIG-1 gene expression) and sites of production can be expected to generate different local patterns, so we must expect some clinical and pathological dissimilarities between systemic diseases that share this common fundamental origin.

TNF generation and circulating levels are increased in influenza,[17] particularly so for influenza caused by the more pathogenic strains. The evidence linking the excess cytokine concept with influenza disease will be well-known by most readers. In brief, influenza A virus stimulates the release of TNF from macrophages,[18] and the recent avian strain induces production of more TNF from human macrophages than do a range of less virulent strains of human influenza.[19] Likewise, this H5N1 influenza virus induces an inflammatory cytokine response in primary cultures of human alveolar and bronchial epithelial cells.[20] H5N1/97 upregulates TNF mRNA levels and TNF-related apoptosis-inducing ligand (TRAIL) in human monocyte-derived macrophages,[21] and higher levels of inflammatory cytokines and chemokines are associated with a fatal outcome.[22] Moreover, a reconstructed version of the strain of influenza virus responsible for massive human mortality in 1918–1919, but not non-virulent constructs or strains, induces a strong and prolonged pro-inflammatory cytokine response during the fatal infections it causes in mice [23] and macaque monkeys.[24] The literature's emphasis on TNF may be artificial, but it is now accepted as the progenitor of a cytokine superfamily, and is demonstrated to be a master regulator of the network of mediators it induces and interacts with.[25]

Thus Fedson's proposal – that any agent known to reduce inflammatory cytokine production and to ameliorate any one of the diseases or conditions mentioned earlier warrants testing in the others – is logical and compelling. Examples are two peroxisome proliferator-activated receptor (PPAR) agonists: gemfibrozil, a fibrate (PPAR-α agonist), reported

by our group to reduce mortality in mouse infection with a H2N2 strain of influenza A[26] and rosiglitazone, a glitazone (PPAR-γ agonist) that does the same in a mouse model for malaria.[27] Both classes of agents reduce inflammatory cytokine production, largely through antagonising the signal transducer, nuclear factor-kappaB (NFκB).[28]

The immunosuppression that can accompany influenza[29] is in fact characteristic of systemic inflammatory disease in general. It is much studied, in terms of cytokine imbalance, in conditions such as sepsis,[30] malaria,[31] trypanosomiasis,[32] and trauma.[33] In malaria, for example, its mechanism has been shown to depend on nitric oxide,[34] a downstream mediator of TNF, which inhibits the function of dendritic cells in malaria, thus limiting antigen presentation.[35] Thus, apart from its clinical relevance as the cause of the secondary bacterial pneumonia often seen in severe influenza, as Fedson discusses, this immunosuppression is a reliable, though indirect, indicator that influenza belongs to the family of conditions caused by excess cytokine production.

Likewise, the rarity of pulmonary oedema in childhood compared with adult influenza,[36] malaria,[37] and trauma,[38] also casts influenza into the same cytokine-mediated mould as malaria and sepsis. Already observed differences in the anti-inflammatory versus pro-inflammatory cytokine ratios between paediatric and adult macrophages stimulated with LPS[39] can plausibly be attributed to differences in PPAR function, as its activation is prolonged in young mice compared with older mice.[40] These insights can only be appreciated if influenza scientists seek, as Fedson urges, the expertise of researchers outside of their immediate discipline.

Others have suggested that any treatment directed against the inflammatory cytokines that cause illness will also inhibit the protective innate response against the virus. This is a valid possibility, as TNF has been reported to exert an *in vitro* effect against influenza virus in human epithelial cells.[41] But what happens *in vivo* is what matters, and others have found that anti-TNF antibody improves experimental influenza disease without influencing virus clearance.[17,42] With close to a million patients having received long-term TNF-neutralising drugs for rheumatoid arthritis or Crohn's disease by 2004,[43] and a call being made in that year for alertness to the possibility of hepatitis or HIV exacerbation,[44] so far as we are aware there are as yet no reports of enhancement of viral disease, including influenza. Likewise, we are not aware of any reports of viral enhancement in patients taking fibrates, glitzones or statins for other reasons. While not as powerful as anti-TNF therapy, these less specific agents are advantageous when the target cytokines are not yet fully defined, as they inhibit a range of them.

Certainly, the simplicity and logic embodied in Fedson's approach to the practical treatment of severe influenza should capture the attention and imagination of researchers interested in intractable infectious disease.

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