COVID-19 IS A MUCOSAL DISEASE

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The first principal of medicine I learnt as a medical student, was “understand the process, understand the disease”. Pandemics challenge many of the basic principles of medicine: Covid is no exception. The fundamental principle most poorly understood in my experience, has been recognition of Covid as an infection of the mucosal space of the respiratory tract, the consequences of which define the pattern of disease and the impact of vaccination aimed at its prevention. The corollary is that the character of infection is determined primarily by the relationship between the virus and the host mucosal immune response.

A summary of the relevant points:

1. Covid is a viral infection of the respiratory tract mucosal space. As such its natural history is dictated by the relationship between the SARS-Cov-2 virus, and the mucosal immune response.
2. Distinctive characteristics of the mucosal immune response to SARS-Cov-2 include: a non-inflammatory protective response; and a dominance of immune suppression in the mucosa and systemic lymphoid tissue.
3. Clinical outcomes of this “host-parasite” relationship include:
    a. Significant inflammatory disease only when the mucosal immune response fails to contain the virus within the bronchus compartment, and the virus interacts with the pro-inflammatory systemic immune response.
    b. As with influenza, vaccination causes a shift from severe to mild/asymptomatic disease, of relatively short duration.
    c. The systemic immune response to the virus and to its vaccine, is the net balance between positive protection, and negative suppression. Repeated short-spaced “boosters” cause reducing periods of protection, followed by suppression and “negative” protection. Cumulative “suppression” could last years, as it does

with allergy desensitisation, severely compromises planned seasonal vaccination.

4. Current mRNA vaccines are experimental. Spike protein is produced throughout the body in an uncontrolled way, and may create immune and toxic damage to endothelium. Reports of adverse events, require analysis as do those of genetic damage.
5. Future vaccination strategy requires spike protein antigen-based vaccines using “non-toxic” epitopes, or nucleocapsid antigens. Widespread availability of safe, cheap and effective re-purposed drugs would greatly facilitate development of safe “spacing” for booster injections.

INTRODUCTION

With respect to Covid, outcomes range from asymptomatic disease when mucosal immune mechanisms confine the virus to the mucosal compartment, to an overwhelming cytokine storm, multi-organ failure and death when the local response fails to restrict virus to the bronchus. Virus enters the gas exchange apparatus which is protected by the systemic immune system where it can trigger an uncontrolled inflammatory systemic immune response, leading to pneumonia and systemic virus spread (1)

The objective of this essay is to discuss the frame within which the “Covid-immune” relationship shapes clinical outcome, and how vaccination impacts on this outcome. Numerous studies on aspects of the immune response in Covid have been published (1). Essentially all address detail in terms of molecular and cellular responses to infection. The studies are largely in isolation without a connect to the mucosal compartment nor do they separate early from late disease. Given the redundancy that characterises inflammatory pathways, the relevance of many findings to clinical events is vague.

To place the immunopathogenesis of Covid in a clinical context, viral-host relationships can be viewed in sequence: viral binding to pattern recognition receptors within the mucosa of the airways; viral driven adaptive/innate immunity within the mucosal compartment; and virus within the gas exchange

apparatus interaction with systemic immune mechanisms. Comment will also be made on the role of Spike protein in causing cell damage and its reaction with the immune response and immunology of vaccination.

1. **Viral infection of the mucosal compartment – binding to pattern recognition receptors (PRR's) (2)**

PRR's on both cell membranes such as the family of Toll-like receptors and inflammasomes and within the cell cytoplasm such as NOD-like receptors, bind to a diverse range of molecules released following Covid infection of the airways: Damage-associated Molecular Patterns or DAMPS, and Pathogen-associated Molecular Patterns or PAMPS. These multiple stimuli initiate single pathway responses involving signalling systems such as NF-kB, to produce a range of cytokines that mediate an inflammatory response. Two relevant to Covid are interferon type 1 as a powerful early control of viral replication and a determinant of viral load within the airways, and "immunothrombosis" or the formation of microthrombi acting to limit spread of pathogens. Here the key mechanisms involved are the expression of "tissue factor" on the surface of monocytes and a "neutrophil extracellular trap" (a network of DNA and other factors secreted from activated neutrophils) (3).

The non-specific nature of damage caused by innate immune pathways, underpins their dual involvement in host protection, and host damage. In Covid, functional deficiency in IFN type 1 due to gene defects or autoantibodies, has been identified in 10-15% of those with severe disease, but not in mild disease or normal controls (4). This suggests an important role for type 1 IFN in controlling the load of virus, which in turn is a determinant of disease severity and spread(5). On the other hand, excessive and inappropriate PRR activation promotes inflammation and microthrombi, features of Covid pneumonia. The tight link between adaptive (specific activation of T and B lymphocytes) and innate (non-specific humoral and cellular factors that both influence adaptive immunity, and mediate effector function) immunity includes control mechanisms that limit damage to targets. Failure to control innate immunity, leads to host damage. This inappropriate and excessive inflammatory response is known as "hypersensitivity disease".

Recent studies show the primary innate immune response to DAMPs and PAMPS is controlled by T reg cells(6). A network of dendritic cells within the mucosa of the airways are positioned to limit mucosal inflammation. When activated, they migrate to regional lymph nodes where they present antigen to T cells and direct their maturation largely into T reg cells(7) characterised as FOXP3+ve cells.. These migrate to the respiratory mucosa, and to systemic lymphoid tissues where they suppress activated innate immunity through secretion of IL-10 and TGF-B, and through cell-cell contact(8).

In conclusion, the damage caused by Covid infection of epithelial cells of the respiratory mucosa reflects a balance of protection/damage following DAMP and PAMP driven innate immunity and its control by T reg cells generated via a mucosal network of dendritic cells. Type 1 IFN has attracted most interest due to its reduction in advanced Covid (4,9). However, in the same study, IL-10, a mediator of suppression, was increased in nasal secretions reflecting this balance.

2. Viral infection of the Mucosal compartment: the Mucosal Immune Response.

Tom Tomasi in 1965 identified IgA as the dominant antibody in secretions to initiate the modern science of mucosal immunology (10). Four pioneers in this immunological awakening, drew attention to the failure to recognise the importance of the mucosal immune system in its role in Covid-19 infection(11), In their review, they focussed on the generation of IgA and IgG antibody by B lymphocytes generated within aggregated lymphoid tissue in the wall of the pharynx, which migrated respectively to mucosal tissues and peripheral lymph nodes using specific receptor systems. Several additional “system” discoveries emphasised the importance of the handling of Covid by the mucosal immune system. First, Bienenstock and his team showed the importance of a “common mucosal system” in the generation of IgA antibody in respiratory tract secretions(12). These lymphocytes migrated through the blood stream to the bronchus mucosa, as the main source of IgA within the bronchus. Second, T cells participated in this circuitry(13). Surprisingly T cells were shown to be the

main mechanism of airways protection by recruiting and activating pathways of innate immunity. The “pulse” of adaptive immunity following aspiration of Covid virus into the gut is suppressed by a wave of T reg cells generated from the dendritic cell carpet (8) and from the intestinal mucosa /Peyer’s patches (14). The protective innate immune mechanisms activated by this adaptive immunity “pulse” is maintained by the phenomenon of “learned innate immunity”. This phenomenon was first shown when neutrophils recruited and activated in the mucosa following antigen stimulation of Peyer’s patches(15), had enhanced activity and prolonged lifespan maintained by an autocrine loop involving IL-1(16). This bronchus-gut connection in man is activated within days of Covid infection, and is highly efficient, confining pathogens to within the bronchus compartment(17).

Resident antigen-specific T- and B-cells found in the mucosa following lung infection are generated as “cell pulses” from Peyer’s patches following antigen aspiration(12,18). Subjects over 65, especially men, mobilise this protection loop less efficiently, enabling higher loads of virus to accumulate, with more severe disease(19). Immune senescence has also been noted in the systemic immune response to Covid vaccination. Older subjects have a delayed IgG antibody and T cell response to Covid vaccines(20).

A major difference between mucosal and systemic immune responses relates to their respective roles in controlling exposure to microbes: systemic immunity maintains a sterile internal environment through a capacity to trigger an explosive innate immune response, regulated largely by elimination of the eliciting antigen; mucosal immunity faces the myriad of microbes colonising mucosal surfaces. A highly complex networking cellular system balances a dynamic that requires control of the commensal “microbiomes” at all exposed surfaces, identification and eradication of pathogens, and a mucosal and systemic mechanism to prevent inflammatory response to “leaked” environmental antigen(8).

A governing principal is that immune outcome is influenced by the route of antigen presentation. Early studies focussed on the gut with chemical haptens. The Sulzberger-Chase phenomenon(21) described the suppression of dermal

contact hypersensitivity to sensitising agents such as picryl chloride, by feeding the agent. This initiated studies on mucosal tolerance, or the active process of mucosal and systemic immune unresponsiveness to ingested or inhaled antigens(22). Most focussed on oral tolerance and the generation of T reg cells, though similar mechanisms were found within the airways (22) Systemic suppression by bronchus T cells in man was the first demonstration of "suppressor" T cells in tissues(23). Mucosal tolerance is the antigen specific non-response to antigen exposure via mucosal or systemic routes (8). T reg cells can be stimulated by antigen. Proximity to target T cells is required for cytokines such as IL-10 and TGF B, or "cell-to-cell" contact, to downregulate responses. Bystander suppression can occur(8,22) . In subjects with Covoid-19, a high frequency of cross-reacting B- and T- cell reactivity to seasonal Corona viruses, reflect long standing sensitisation following earlier infections (24), to prime mucosal and systemic immune responses to Covid infection and to vaccination.

3. Escape of Covid virus into the gas exchange apparatus.

The gas exchange apparatus of the lungs is protected by the systemic immune system, and the outcome of penetration of Covid antigen into the alveolar space is determined by the dynamic of immune complex formation between antigen and antibody. Antigen excess (in the "immune naïve") promotes inflammation and viral pneumonia, while antibody excess (as seen post vaccination) is protective. Cross-reactive T cells from historic Corona virus infections and T cells generated by the Covid infection modulate outcome(24). A third factor is the toxicity of the virus Spike protein which damages endothelium to promote coagulation(25). Clotting within the microvasculature of the gas exchange apparatus is a characteristic of Covid pneumonia. The pathology and immunology of Covid pneumonia, cytokine storm and multisystem disease has been extensively covered, and will not be further discussed in this review(1).

4. The immunology of vaccination.

Early enthusiasm followed IgG antibody responses to Covid vaccination with both antigen and genetic vaccines. Seroconversion of around 90% failed to be tempered by years of experience with influenza vaccination. Corona and influenza viruses cause seasonal infections subject to antigen drift, which become pandemic when mutants enable escape from the bronchus. Injected influenza vaccines shift disease spectrum from severe disease to less severe disease and asymptomatic infection, with efficacy of about 6 months(26). High recorded early clinical protection following the initial Covid vaccine trials, was in part due to the non-specific protection that follows vaccination due to polyclonal T cell activation(27). Both influenza and Covid vaccines stimulate specific systemic T and B cells, but little immune protection within the mucosal space(9). Covid vaccination appeared more effective than seasonal influenza vaccines, as in pandemic disease, protection is mediated by systemic immunity.

The question is: why doesn't the IgG response and immune protection following Covid vaccination more resemble those with measles and other systemic infections?

The answer is that the primary mucosal infection influences systemic immunity through seeding of T reg cells, as discussed above. These T reg cells respond to antigen stimulation and have a "by-stander" effect (8). This has been documented with blunting of antibody measured following vaccination of those with a history of Covid infection(28). Current public health strategy is based on experience with classic systemic vaccines, which are less influenced by T reg cells. The policy of repeated vaccination predictably is giving ever decreasing periods of protection followed by specific immune suppression associated with negative protection. The latter group are more liable to get infected than unvaccinated controls. For example the UK data show initial protection of about 6 months, suggest the wave of reversal from negative to positive protection, lasts about 2 months with subsequent reversal to "negative protection" and even more severe disease (29). A view that describes this data as evidence of "destruction of the immune apparatus" (30) ignores study of oral tolerance, food allergies and desensitisation for airways allergic disease. Clinical benefit of pollen desensitisation given subcutaneously

pre-season for 2-3 years, is antigen-specific, and persists for years(31). The current practise of repeated vaccination with accumulation of immune suppression and a drift away from protection against new variants (29), is concerning, as it risks long term tolerance to Covid-19 infection (and other corona virus infections), and failure of future seasonal vaccines. The importance of vaccination spacing to prevent immune suppression, is critical. The annual influenza dose covering the peak influenza season appears to be a good model.

Most Covid vaccines to date have been either a DNA vector, or a mRNA vaccine. There is no evidence they give better protection than antigen vaccines. mRNA vaccines code for uncontrolled systemic production of Spike protein with three outcomes. First the dose of antigen is completely unknown. Second a toxic molecule circulates, causing unknown damage to vessels, myocardium and neural tissues(25). Third, Spike protein is expressed on tissues throughout the body, and persists in blood for up to 2 weeks (32) with the potential of behaving as an "autoantigen" – This remains unproven, but German pathologists describe characteristic lymphocytic infiltrations and small vessel vasculitis as characteristic lesions in most post-mortems conducted on subjects following vaccination (33). A controversial but critically important area, that requires clarification and further study(34).

CONCLUSION.

The purpose of this review is to put in context the importance of considering Covid as an infection of a mucosal space. The evolution of disease and the outcome of vaccination can best be understood in terms of the dual positive and negative immune outcomes of mucosal infection, influenced by previous cross-reactive corona virus infections. The impact of tolerogenic cells limiting vaccine immunity, identifies the potential danger of repeated booster vaccinations, currently noted in the UK. The importance of spacing vaccination to prevent accumulated immune suppression, should be part of future management strategy. Cheap, safe & available re-positioned drugs effective in early treatment of Covid can no longer be ignored as a part of any strategic plan that includes spacing of vaccination shots (35).

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